# BLA Clinical Review Memorandum

| Submission Properties | Description |
|---|---|
| Application Type | Supplemental Biologics License Application |
| STN | 125471/230 |
| CBER Received Date | January 11, 2018 |
| PDUFA Goal Date | November 11, 2019 (Non-PDUFA product) |
| Division / Office | DVRPA/OVRR |
| Priority Review (Yes/No) | No |
| Reviewer Name | Joohee Lee, MD |
| Review Completion Date / Stamped Date | November 9, 2018 |
| Supervisory Concurrence | Roshan Ramanathan, MD, MPH<br>Acting Branch Chief, Clinical Review Branch 1 |
| Applicant | Stallergenes SAS |
| Established Name | ORALAIR® (Sweet Vernal, Orchard, Perennial Rye, Timothy, and Kentucky Blue Grass Mixed Pollens Allergen Extract)<br>Tablet for Sublingual Use |
| (Proposed) Trade Name | ORALAIR |
| Pharmacologic Class | Allergen extract |
| Formulation(s), including Adjuvants, etc. | Tablet |
| Dosage Form(s) and Route(s) of Administration | Sublingual tablet |
| Dosing Regimen | To be initiated 4 months prior to the onset of each grass pollen season<br>For children and adolescents 5 through 17 years of age:<br>Day 1: One tablet of 100 IR<br>Day 2: Two tablets of 100 IR<br>Day 3 onwards: One tablet of 300 IR daily<br><br>For adults 18 through 65 years of age: 300 IR daily |
| Indication(s) and Intended Population(s) | ORALAIR is an allergen extract indicated as immunotherapy for the treatment of grass pollen-induced allergic rhinitis with or without conjunctivitis confirmed by positive skin test or in |

| Submission Properties | Description |
|---|---|
| | vitro testing for pollen-specific IgE antibodies for any of the five grass species contained in this product. ORALAIR is approved for use in persons 5 through 65 years of age. |
| Orphan Designated (Yes/No) | No |

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## GLOSSARY

| | |
|---|---|
| AD | Atopic dermatitis |
| AE | Adverse event |
| APAC | Allergenic Products Advisory Committee |
| AR | Adverse reaction |
| ARC | Allergic rhinitis with or without conjunctivitis |
| BLA | Biologics License Application |
| CBER | Center for Biologics Evaluation and Research |
| CDC | Centers for Disease Control and Prevention |
| CMC | Chemistry, Manufacturing, and Controls |
| CS | Combined Score |
| EoE | Eosinophilic Esophagitis |
| IgE | Immunoglobulin E |
| IR | Index of Reactivity |
| PLLR | Pregnancy and Lactation Labeling Rule |
| PP | Per-protocol |
| PREA | Pediatric Research Equity Act |
| RMS | Rescue Medication Score |
| RTSS | Rhinoconjunctivitis Total Symptom Score |
| SAE | Serious Adverse Event |
| SCIT | Subcutaneous Immunotherapy |
| SLIT | Sublingual Immunotherapy |
| SPT | Skin Prick Test |

## 1. Executive Summary

ORALAIR® is a tablet of comprised of extracts from five grass pollens: Kentucky bluegrass (*Poa pratensis*), Orchard (*Dactylis glomerata*), Perennial rye (*Lolium perenne*), Sweet vernal (*Anthoxanthum odoratum*) and Timothy (*Phleum pratense*). ORALAIR was initially approved in 2014 for treatment of grass pollen-induced allergic rhinitis with or without conjunctivitis confirmed by positive skin test or in vitro testing for pollen-specific IgE antibodies for any of the five grass species contained in ORALAIR. ORALAIR was approved for use in persons 10 through 65 years of age. With this Biologics License Application supplement (sBLA), Stallergenes seeks licensure of ORALAIR in children 5 through 9 years of age.

Prior to the licensure of ORALAIR, the Allergenic Products Advisory Committee (APAC) discussed the adequacy of the clinical data to support safety and effectiveness of ORALAIR in children 5 through 9 years of age. The clinical development program included a double-blind placebo-controlled Phase 3 study (VO52.06 EU) conducted in 278 children and adolescents 5 through 17 years of age who were randomized 1:1 to receive either placebo (n=139) or ORALAIR (n=139) for four months prior to the onset of and throughout the grass pollen season. The study met its pre-specified primary endpoint success criterion, which was to demonstrate a reduction in the average rhinoconjunctivitis symptom score (RTSS) between the treatment and placebo arms of at least 20%. The efficacy data from V052.06 were considered adequate to support the effectiveness of ORALAIR in children 5 through 17 years of age. For the intent-to-treat population, the point estimate for the difference in the average RTSS between ORALAIR and placebo groups was -25.6% (95% CI: -40.4%, -10.3%). In a *post hoc* subgroup efficacy analysis of data from children 5 through 9 years of age performed by CBER, ORALAIR was observed to have a -47.1% percent reduction in the daily RTSS score between treatment arm and placebo (95% CI: -75.3% -19.0%); a -26.5% reduction in the daily Rescue Medication Score (-60.2%, 7.1%); and a -34.7% reduction in the daily Combined Score (95% CI: -61.6%; -7.7%). Similar calculations in the children and adolescents 10 through 17 years of age were conducted and are presented in the body of this review. Results do not suggest that efficacy is different in younger children than in older children or adolescents.

Since Study V052.06 EU included only 57 children 5 through 9 years of age, this study was not considered adequate to support safety of ORALAIR in this age group. Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), Stallergenes was required to conduct Study 140224 to evaluate the safety of ORALAIR in children 5 through 9 years of age.

This sBLA includes safety data from an open-label multi-center study of ORALAIR (Study 140224/ Protocol SL 74.14) conducted in Europe. The study included 307 children 5 through 9 years of age with grass pollen-related allergic rhinitis and allergic rhinoconjunctivitis (ARC) confirmed by positive skin prick test or *in vitro* testing for grass pollen-specific IgE. The primary objective of the study was to evaluate safety and tolerability during the first 30 days of treatment. Approximately 56% of subjects had at least one adverse reaction, the majority of which were mild or moderate in severity. The

most common adverse reactions were throat irritation (22.8%), oral pruritus (11.7%), oral paresthesia (11.1%), tongue pruritus (8.1%), mouth edema (6.2%), cough (6.2%), ear pruritus (5.2%), oropharyngeal pain (4.2%), eye pruritus (4.6%), lip edema (3.3%), vomiting (2.6%), tongue edema (2.3%), abdominal pain (2.3%), oral discomfort (2.3%), and ocular hyperemia (2.0%). Sixteen subjects (5.2%) prematurely withdrew from the study due to an adverse event. There were two serious adverse events (SAE), anaphylaxis and angioedema. Both were characterized as "probable/likely" due to ORALAIR. There were no deaths.

The safety data submitted to this supplement from Study 140244 (Protocol SL74.14), in conjunction with the efficacy data from Study V052.06, support licensure of ORALAIR in children 5 through 9 years of age. The frequencies of local application site reactions, particularly throat irritation and oral pruritus, among the 5- through 9-year-olds were comparable to that of adults and older children and adolescents. With respect to efficacy, the pre-licensure data from V052.06 were considered representative of children and adolescents 5 through 17 years of age.

### 1.1 Demographic Information: Subgroup Demographics and Analysis Summary

There was balanced representation of 5-, 6-, 7-, 8-, and 9-year-olds among the 307 study participants. Over 70% of the children were male, which is consistent with the greater prevalence of allergic rhinitis among males in childhood. Most were polysensitized (n=170) and approximately 36% had asthma. Data on race and ethnicity were not collected in Study 140244. Subgroup analyses with respect to safety were presented with respect to age, males compared to females, those with asthma compared to those without, and those who were mono-sensitized to only grass pollen(s) compared to those who were sensitized to other aeroallergens (i.e., poly-sensitized). No substantial differences in the safety profile of ORALAIR (with respect to adverse events and their severity, rates of recurrence, and corresponding system organ class) were noted based on age, sex, asthma status, sensitization status.

## 2. Clinical and Regulatory Background

### 2.1 Disease or Health-Related Condition(s) Studied

Allergic rhinitis with or without conjunctivitis (ARC) falls within a spectrum of chronic diseases driven by allergen-induced IgE-mediated and cell-mediated immune responses. ARC presents as a constellation of nasal and non-nasal symptoms including sneezing, anterior and posterior rhinorrhea, congestion, and ocular itching and congestion. Common environmental triggers include perennial allergens, such as house dust mites and cat dander, and seasonal allergens, such as grass and ragweed pollens. Polysensitization is common among individuals with allergic rhinitis; reported rates of prevalence of polysensitization in populations seeking medical care for allergic rhinitis range between 31% to 74% (Migueres, 2014). Allergic rhinitis commonly coexists with asthma, which typically develops after allergic rhinitis. It has been estimated that about

20 to 40% of individuals with allergic rhinitis also have asthma. Conversely, about 30 to 80% of individuals with asthma have allergic rhinitis (Compalati et al. 2010).

Allergic rhinitis is among the most common diseases affecting adults. According to a recent set of guidelines, allergic rhinitis is the most common chronic disease in children in the United States. According to the Centers for Disease Control and Prevention (CDC), in the U.S., approximately 16 million adults (6.5%) and 5.5 million children and adolescents (7.5%) reported "hay fever," and 7.6 million children and adolescents (10.3%) reported "respiratory allergies" ("Allergy and Hay Fever"). The burden of allergic rhinitis in Europe is also substantial. In a 2004 study, approximately 23% of adults (19% in Spain, 29% in Belgium) were found to have clinically confirmed allergic rhinitis. Furthermore, grass pollen was noted to be the most common cause of respiratory allergies and associated with over 50% of allergic rhinitis cases (Bachau and Durham 2004).

## 2.2 Currently Available, Pharmacologically Unrelated Treatments for the Proposed Indication

The treatment for ARC, allergen avoidance, is usually hard to achieve and sustain. Therefore, clinical management typically relies on combined regimens of intranasal steroids and oral, intranasal, and ocular antihistamines. In addition, nasal rinsing with saline using over-the-counter kits is commonly recommended for symptom management.

## 2.3 Safety and Efficacy of Pharmacologically Related Products

Unlike avoidance and symptomatic therapy, allergen-specific immunotherapy offers the potential to reduce allergic symptoms and decrease the need for symptomatic treatment by increasing an individual's tolerability to a specific allergen.

GRASTEK® is the other grass pollen SLIT product. It was licensed in 2014 and is indicated for the treatment of grass pollen-induced allergic rhinitis with or without conjunctivitis confirmed by positive skin test or *in vitro* testing for pollen-specific IgE antibodies for Timothy grass or cross-reactive grass pollens. GRASTEK is approved for use in persons 5 through 65 years of age. Like ORALAIR, most of the adverse reactions in young children were local reactions, such as oral pruritus (24.4% vs 2.1% placebo), throat irritation (21.3% vs 2.5%) and mouth edema (9.8% vs 0.2%). The symptom and medication use scoring systems, Daily Symptom Score (DSS) and Daily Medication Score (DMS) used in the efficacy studies of GRASTEK were not the same as those used in the efficacy sutdies of ORALAIR. Rather than the symptom score, FDA considered the composite of both symptom and medication use scores (i.e., Combined Score) as the preferred endpoint for evaluating efficacy. The efficacy of GRASTEK in children and adults was demonstrated in natural field studies, with a point estimate of the Total Combined Score (TCS) of -26% and -23% and a lower bound of the 95% confidence interval -10.1% and -13.0%, respectively.

There are 8 standardized grass extracts approved by the FDA in 1997 for subcutaneous immunotherapy (SCIT) for the reduction of grass pollen-induced allergic symptoms confirmed by positive skin test or by *in vitro* testing for pollen-specific IgE antibodies for Bermuda grass pollen, Kentucky Blue (June) grass pollen, Meadow Fescue grass pollen, Orchard grass pollen, Perennial Rye grass pollen, Redtop grass pollen, Sweet Vernal grass pollen, or Timothy grass pollen.

Standardization refers to potency in terms of Bioequivalent Allergy Units (BAU). The eight standardized extracts include the five grass pollens in ORALAIR, which are Kentucky bluegrass (*Poa pratensis*), Orchard (*Dactylis glomerata*), Perennial rye (*Lolium perenne*), Sweet vernal (*Anthoxanthum odoratum*) and Timothy (*Phleum pratense*). The other three are Bermuda *(Cynodon dactylon),* Meadow fescue (*Festuca elatior*), and Red top (*Agrostis alba*). As with the SLIT products, SCIT is contraindicated in persons with severe, unstable, or uncontrolled asthma. Unlike SLIT products, there is no defined dose or regimen (i.e., standard versus accelerated) for SCIT, which is tailored to an individual patient and varies from one allergist-immunologist to another. In poly-sensitized individuals, SCIT prescriptions may be one or two different mixture of multiple allergens. In general, systemic allergic reactions are more common with SCIT. As stated in the package insert, the most common adverse reactions occurring in over 26 to 82% of all patients who receive SCIT are local adverse reactions at the injection site (e.g., erythema, itching, swelling, tenderness, pain). Systemic adverse reactions, occurring in $\leq$ 7% of patients, include generalized skin erythema, urticaria, pruritus, angioedema, rhinitis, wheezing, laryngeal edema, and hypotension. Effectiveness of these extracts is based on a 1985 publication by the Panel on Review of Allergenic Extracts, an advisory committee to the U.S. FDA (Implementation of Efficacy Review, Allergenic Extracts, Federal Register 1985).

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

Stallergenes was first granted authorization to market ORALAIR in Germany in 2008 as a "named subject product," which is considered an intermediate between investigational versus licensed status. As part of this authorization, Stallergenes conducted two post-authorization safety studies (PASS) in 2008 and 2009 of 920 children and adolescents, 318 of whom were 5 through 9 years of age. The most common adverse reactions reported from the 2009 study were application site reactions, throat irritation (14.3%), oral paresthesia (6.2%), oral pruritus (4.9%), and mouth edema (4.6%). Six SAEs were reported in 6 patients (4 children and 2 adolescents). These data are consistent with the findings from the double-blind, placebo-controlled studies that evaluated the safety of ORALAIR in children 5 through 17 years of age conducted prior to the initial U.S. licensure of ORALAIR in 2014.

At the time of the initial approval of ORALAIR by FDA, Stallergenes committed to conduct a postmarketing study (Study 140225; Protocol SL76.14) to describe the safety profile in approximately 6,000 patients 10 through 65 years of age receiving ORALAIR approximately 4 months prior to and throughout the grass pollen season. Stallergenes submitted a final clinical study report in June 2018 (STN 125471/251; received June 30, 2018). Due to limited sales of ORALAIR during grass pollen seasons between 2015 and

2017, the study could only enroll 2,814 participants. Safety data were obtained for 390 subjects from 92 physicians who completed surveys. Over three grass pollen seasons, 6 participants had 7 adverse drug reactions that required medical attention, but none required hospitalization. Three were systemic adverse reactions (generalized cutaneous reaction; throat tightness and chest discomfort; severe throat tightness) that resolved with epinephrine use. There were 2 cases of oral pruritus that resolved with oral antihistamines, 1 case of cutaneous pruritus that resolved with oral antihistamines, and one case of dyspepsia that resolved without any medication. There were no cases of eosinophilic esophagitis.

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

Pre-Submission

- May 2011: CBER convened an Allergenic Products Advisory Committee (APAC) to discuss topics pertaining to the assessment of efficacy of SLIT products, including statistical parameters for efficacy endpoints, standards for clinically meaningful results, and the use of AECs and its advantages over the natural exposure study design. (*APAC meeting materials and minutes, May 12, 2011*. https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/AllergenicProductsAdvisoryCommittee/ucm552785.htm)

- December 2013: APAC convened to discuss the Biologics License Application (BLA) for ORALAIR, which included data from 4 field studies (one conducted under an IND) and one allergen exposure chamber (AEC) study. The approval was limited to 10- through 65-year-olds because five of the 10 committee members did not find a safety database of 57 in the younger children was sufficient for concluding that ORALAIR was safe in 5- through 9-year-olds. (*APAC meeting materials and minutes, December 11, 2013.* https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/AllergenicProductsAdvisoryCommittee/ucm552785.htm).

  March 2014: ORALAIR was licensed in persons 10 through 65 years of age. Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), Stallergenes was required to conduct Study 140224 to evaluate ORALAIR in children 5 through 9 years of age.

- There were no meetings prior to the submission of this efficacy supplement.

## 3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

### 3.1 Submission Quality and Completeness

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

3.2 Compliance With Good Clinical Practices And Submission Integrity

There are two manufacturing locations (30004015717 and (b) (4) ) in France associated with Study 140244. Neither of these sites have ongoing or pending investigations or compliance actions. Therefore, the Office of Compliance and Biologics Quality, Division of Case Management did not perform any inspections for this supplement.

3.3 Financial Disclosures

| | | |
|---|---|---|
| Covered clinical study (name and/or number):<br>An observational study of Oralair® (Grass pollen allergen extract from: Cocksfoot, Sweet Vernal, Rye Grass, Meadow Grass, Timothy) tablet for sublingual use in children 5 to 9 years of age with grass-pollen-induced allergic rhinitis with or without conjunctivitis (SL 74.14) | | |
| Was a list of clinical investigators provided: | Yes ☒ | No ☐ (Request list from applicant) |
| Total number of investigators identified: 3 coordinating investigators for each country (total of 110 site investigators) | | |
| Number of investigators who are sponsor employees (including both full-time and part-time employees): 0 | | |
| Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0 | | |
| If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):<br>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____<br>Significant payments of other sorts: _____<br>Proprietary interest in the product tested held by investigator: _____<br>Significant equity interest held by investigator in sponsor of covered study: _____ | | |
| Is an attachment provided with details of the disclosable financial interests/arrangements: | Yes ☐ | No ☐ (Request details from applicant) |
| Is a description of the steps taken to minimize potential bias provided: | Yes ☐ | No ☐ (Request information from applicant) |
| Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0 | | |
| Is an attachment provided with the reason: | Yes ☐ | No ☐ (Request explanation from applicant) |

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

4.1 Chemistry, Manufacturing, and Controls (CMC)

This submission did not include new CMC data. Please see the CMC review by Jennifer Bridgewater for details.

### 4.4.1 Mechanism of Action

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

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

4.5 Statistical

The CBER biostatistician confirmed the accuracy of the *post hoc* analyses of efficacy in 5 through 9-year-old subjects compared to 10 through 17-year-old subjects from the prelicensure study VO52.06. Please see the Biostatistical review by Jennifer Kirk for a detailed discussion of the post-hoc analyses of the primary and secondary efficacy endpoints by age group.

4.6 Pharmacovigilance

Stallergenes did not propose any changes to the pre-existing pharmacovigilance plan (PVP) for ORALAIR. The CBER reviewer from the Division of Epidemiology (DE) in the Office of Biostatistics and Epidemiology (OBE) concluded that the PVP in place was adequate. This determination was based on the review of Study 140244, ORALAIR postmarketing periodic adverse experiences report (April 1, 2017 through March 31, 2018), OBE internal safety reports for ORALAIR through December 31, 2017, and published literature related to ORALAIR through August 8, 2018. Please see the Pharmacovigilance review by Dr. Patricia Rohan for details.

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

## 5.1 Review Strategy

Assessment of the safety of ORALAIR in 5- through 9-year-olds was based on safety data from Study 140244. A *post hoc* analysis of efficacy in 5- through 9-year-olds from the pre-licensure study V052.06 was conducted to compare the magnitude of treatment effect with 10- through 17-year-olds.

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

The following documents submitted to this sBLA, as listed by STN and electronic common technical document (eCTD) module or IND number, served as the basis for this review.

- STN 125471/230.0
  - Module 1.14.1 (Draft Labeling)
  - Module 2.5 (Clinical Overview)

- STN 230/230.1 [Module 5.3.5 (Reports of Efficacy and Safety Studies STN 125471/230.1 – draft label in accordance with the Pregnancy and Lactation Labeling Rule (PLLR)]

- STN 125471/230.2
  - Narratives for subjects who had SAEs and AEs leading to study discontinuation
  - Clinical study report and datasets for pre-licensure pediatric study V052.56
  - List of all investigators from the 103 study sites
  - Financial Disclosure form 3454

- STN 125471/230.3 [Response to 5 IR comments]
  - Summary of post-marketing safety data from children 5 through 11 years of age over 9 years,
  - Pregnancy data from pre-licensure clinical development program
  - Data sets for post hoc analyses of efficacy endpoints in children 5 through 9 years of age
  - Safety data retabulation (excluding 52 subjects with missing or unevaluable test results for sensitization)

- STN 125471/230.4, 230.5, 230.7, 230.8, 230.9 [Revised package inserts addressing CBER and Stallergenes comments]

- STN 125471/0
  - Clinical Review
  - V052.06 Clinical Study Report

- STN 125471/(b) (4) [Final report for Postmarketing Study (Protocol SL76.14, Study 140225)]

## 5.3 Table of Studies/Clinical Trials

**Table 1. Clinical trials of ORALAIR in Children 5 through 9 Years of Age**

| ***Study ID***<br><br>*Study design* | *Population* | *Safety endpoints* | *Efficacy endpoints* |
|---|---|---|---|
| **V052.06**<br><br>Placebo-controlled, double-blinded, randomized, multi-center study | N=278[a]<br>Children and adolescents 5 through 17 years of age (including 57 children 5 through 9 years of age) with grass pollen-related ARC for ≥ 2 pollen seasons | Open-ended daily diary cards and physician interpreted AEs during 7 clinic encounters over 10 months | Average Combined Score (CS), the sum of the average Rhinoconjunctivitis Symptom Score (RTSS) and Rescue Medication Use Score |
| **140244**<br>*(Protocol SL 74.14)*<br><br>Open-label multi-center study | N=307 children 5 through 9 years old with grass pollen-related ARC for at least 1 season | Open-ended daily diary cards completed by caregivers and AEs interpreted by physicians (into preferred terms) at a clinic visit after 30 days of ORALAIR | Not assessed |

[a]Eligiblity: Positive skin prick test (SPT) to the 5 grass pollen allergen extract, specific IgE positive to grass pollen (>Class 2); RTSS score ≥12, FEV1>80% normal for those with mild-intermittent asthma
[b] Study evaluated safety during the first thirty days of treatment

## 5.5 Literature Reviewed

- Allergies and Hay Fever. (2016, July 06). Retrieved November 11, 2018, from https://www.cdc.gov/nchs/fastats/allergies.htm

- Akdis M and Akdis CA. Mechanisms of allergen-specific immunotherapy: Multiple suppressor factors at work in immune tolerance to allergens. J Allergy Clin Immunol 2014; 133(3):621-31

- Bachau V and Durham SR. Prevalence and rate of diagnosis of allergic rhinitis in Europe. European Respiratory Journal 2004; 24: 758-764

- Compalati E, Ridolo E, Passalacqua G, et al. The Link Between Allergic Rhinitis and Asthma: the United Airways Disease. Expert Rev Clin Immunol. 2010; 6: 413-423.

- Frati F, Moingeon P, Marcucci F, et al. Mucosal immunization application to allergic disease: sublingual immunotherapy. Allergy Asthma Proc. 2007; 28: 35-39.

- Frohlich M, Pinart M, Keller T, et al. Is there a sex-shift in prevalence of allergic rhinitis and comorbid asthma from childhood to adulthood? A meta-analysis. Clinical and Translational Allergy 2017; 7:44.

- Implementation of Efficacy Review, Allergenic Extracts, Federal Register 1985; 50: 3082-3288.

- Migueres M., et al. Types of sensitization to aeroallergens: definitions, prevalences and impact on the diagnosis and treatment of allergic respiratory disease. Clinical and Translational Allergy 2014; 4:16. Open Access publication. Retrieved from: https://ctajournal.biomedcentral.com/articles/10.1186/2045-7022-4-16

## 6. Discussion of Individual Studies/Clinical Trials

### 6.1 Trial #1

**Study 140224/ Protocol SL 74.14**

#### 6.1.1 Objective

The primary objective was to assess safety and tolerability of ORALAIR in children 5 through 9 years of age with grass-pollen-induced allergic rhinitis with or without conjunctivitis.

#### 6.1.2 Design Overview

Study 140244 was an open-label single-arm multi-center study conducted in Europe. Study subjects were identified by physicians at study sites as candidates for grass sublingual immunotherapy.

#### 6.1.3 Population

This study enrolled 307 children 5 through 9 years of age with grass pollen-related allergic rhinitis with or without conjunctivitis at over 100 clinical sites located in Germany, France, and Austria.

#### 6.1.4 Study Treatments or Agents Mandated by the Protocol

ORALAIR was administered using the pediatric dosing regimen, which begins with one tablet of 100 IR on Day 1, two tablets of 100 IR on Day 2, and one tablet of 300 IR administered daily on Day 3 and thereafter.

### 6.1.5 Directions for Use

ORALAIR is initiated approximately 4 months prior to the expected onset of the grass pollen season. The first dose of ORALAIR needs to be administered in a healthcare setting and the patient should be observed for at least 30 minutes to monitor for signs and symptoms of an acute allergic reaction. If the first dose is tolerated, subsequent doses to children can be administered under adult supervision. The tablet should be removed from packaging when ready to use, and immediately placed in the mouth and held underneath the tongue for at least one minute, until the tablet is completely dissolved, and hands should be washed after handling ORALAIR. To avoid swallowing allergen extract, food or beverage should not be taken for 5 minutes following dissolution of the tablet.

### 6.1.6 Sites and Centers

This multi-center study had 103 sites in Austria, France, and Germany. Most subjects were from Germany (n=172) and France (n=126).

### 6.1.7 Surveillance/Monitoring

Study participants completed two clinic visits. The first visit (Day 1) was when the first dose of ORALAIR (100 IR) was administered. Guardians and parents received a telephone call on Day 4 to remind them to complete an open-ended daily record card. At the second clinic visit (Day 31 to 45), the investigator reviewed the 30 days of safety data with the subjects' caregivers, completed the case report form (CRF), assessed causality, and graded the AEs using the following 3-point grading scale:

- Mild: aware of event or symptom, but easily tolerated and not interfering with his or her usual level of activity
- Moderate: sufficient discomfort to interfere with or reduce his/her usual level of activity
- Severe: significant impairment of functioning; unable to carry out usual activities

### 6.1.8 Endpoints and Criteria for Study Success

Study 140224 evaluated the safety of ORALAIR in children 5 through 9 years of age over the first 30 days of treatment based on an open-ended diary card completed by parents and guardians of the study participants. There were no pre-specified criteria for study success.

### 6.1.9 Statistical Considerations & Statistical Analysis Plan

A sample size of 300 participants provided 95% probability of observing at least one adverse event expected to occur at a frequency of 1%. Safety data endpoints were summarized descriptively using the safety set, consisting of all enrolled children (n=307) who received at least one dose of ORALAIR.

### 6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

6.1.10.1.1 Demographics

**Table 2: Demographics of 307 children 5 through 9 years of age in Study 140244**

| Age | 5 years old | 6 years old | 7 years old | 8 years old | 9 years old |
|---|---|---|---|---|---|
| n (% of 307) | 47 (15.3) | 65 (21.2) | 69 (22.5) | 61 (19.9) | 65 (21.2) |
| Male n (%) | 37 (78.7) | 45 (69.2) | 44 (63.8) | 43 (70.5) | 50 (76.9) |
| Female n (%) | 10 (21.3) | 20 (30.8) | 25 (36.2) | 18 (29.5) | 15 (23.1) |

Source: Adapted from table 10-2 from the Study Report Body (p. 37 of 1380) submitted to STN *125471/230*

> ***Reviewer comment:*** *The predominance of males in this study of young children reflects the skewed prevalence of allergic rhinitis in childhood. A meta-analysis exploring the demographics of allergic rhinitis across age groups reported the male-female ratio in children (0 to 10 years of age) to be 1.25 (95% CI: 1.19; 1.32; n=5 studies). This increased to 1.65 (1.52, 1.78) for allergic rhinitis and concurrent asthma. The ratios shift towards female predominance among adolescents and adults (Frolich M, et al., 2017). The large number of sites (i.e., over 100 sites), each of which enrolled anywhere from 1 to 16 subjects, may also have contributed to the predominance of males in this study.*

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Most of the 307 children enrolled in Study 140244 had a history of allergic symptoms for two consecutive grass pollen seasons, and 75.9% had allergic conjunctivitis. Approximately 36% had asthma. Fifty-two of the children did not have complete testing results to categorize them as monosensitized or polysensitized. Among the 255 children with complete and evaluable test results for sensitization, more were polysensitized (n=179) than monosensitized (n=76). Polysensitized children were co-sensitized to seasonal and perennial allergens, specifically tree pollens (n=101), dust mite allergens (n=75), and animal allergens (n=48).

Approximately 20% (n=63) of the study population had previous medical conditions other than allergic rhinoconjunctivitis and asthma. The most common system organ class (SOC) was Surgical Procedures, namely tonsillectomy and adenoidectomy, followed by Skin and Subcutaneous Tissue Disorders, namely atopic dermatitis (9.0%; n=23), neurodermatitis (2.7%; n=7), and eczema (2.0%; n=5). Eight subjects (2.6%) had Gastrointestinal Disorders, most commonly gastroesophageal reflux (1.3%; n=4). There were single cases of dental caries, dyspepsia, irritable bowel syndrome, and oral cavity fistula.

The most common protocol violation was not abiding by the follow-up visit date range (9.1%; n=28). Six subjects' diary cards were not returned (2.0%), and 5 subjects' caregivers completed the second clinic visit by telephone (1.6%). Five subjects did not meet the inclusion criterion of being naïve to allergen immunotherapy. Three subjects' sensitization status to grass pollen was not evaluable or was negative (1.0%; n=3). In addition, one 10-year-old and two 12-year-olds were inappropriately enrolled.

***Reviewer comment****: Most of the 52 children who were not tested for sensitization to for aeroallergens (other than grass pollen) were from sites in Germany (n=49; 94.2%). Assessment of the breadth of sensitization is informative when assessing the magnitude of allergen-specific treatment on symptoms. Symptom scores in a mono-sensitized individual would provide a cleaner assessment of any allergen immunotherapy since there is no interference from symptoms related to other allergens, particularly perennial allergens. However, since this is a safety study, absence of complete profiles for sensitization is of less concern than it would have been for an efficacy study. To verify that this would not substantially affect the descriptive safety data from Study 14022, CBER requested Stallergenes to provide safety summaries limited to the 255 subjects with data on sensitization to allergens other than grass pollen for comparison with those for all 307 subjects to ensure that the safety profile of ORALAIR was not different in this subgroup. The data submitted in this sBLA indicated that the demographic profiles with respect to age, sex, and concurrent asthma were similar between the subset of 255 children who could be definitively classified as mono-sensitized or polysensitized and the total safety population of 307 children. It was reassuring to note that the frequency of adverse reactions and their associated severity and system organ classes were also similar across groups.*

6.1.10.1.3 Subject Disposition

Approximately 91% of the 307 enrolled children completed the study. Mean treatment exposure was 29 days. Approximately 96% of participants were compliant to treatment (i.e., taking at least 80% of the daily doses). Twenty-seven children (8.8%) dropped out of the study. The most common reason was due to an adverse event (n=16; 5.2%). Nine subjects (3.0%) discontinued for reasons other than an adverse event, and two subjects' (0.7%) guardians withdrew consent.

***Reviewer comment:*** *Over 90% of subjects completed the study. The percentage of subjects who discontinued was < 10% which is consistent with discontinuation rates seen in other studies. Most of the adverse events that led to study dropout were application site reactions (n=13). All were noted to be resolved or resolving at the time of discontinuation. All but one of these adverse events (pyrexia) were causally linked to ORALAIR (ranging from "possible" to "highly probable"). The demographic profile of the children who dropped out due to adverse events mirrored the overall study population. There were more children who were male (n=11) than female, more who were poly-sensitized (n=9 vs. 4 mono-sensitized and 2 unknown), no predominance of specific age, and most did not have concurrent asthma (n=12).*

## 6.1.12 Safety Analyses

6.1.12.1 Methods

Study 140244 evaluated safety during the first 30 days of ORALAIR use in children 5 through 9 years of age.

6.1.12.2 Overview of Adverse Events

A total of 816 AEs was reported in 75.9% (n=233) of the 307 children 5 to 9 years of age, with most occurring under the System Organ Classes (SOCs) of Gastrointestinal disorders (47.6%) and Respiratory, thoracic, and mediastinal disorders (43.3%). The most frequently reported AEs were throat irritation (23.8%), cough (14.3%), oral pruritus (11.7%), oral paresthesia (11.1%), tongue pruritus (8.1%), oropharyngeal pain (7.2%), abdominal pain (6.8%), vomiting (6.5%), and lip edema (6.2%).

Most participants (45.0%) had at least one mild adverse reaction, 66 (21.5%) with at least one moderate adverse reaction, and 10 (3.3%) with at least one severe adverse reaction. There were 15 severe adverse reactions reported in 10 children. The preferred terms included oral pruritus (n=3), mouth edema (n=1), oral discomfort (n=1), oropharyngeal pain (n=1), asthma (n=1), eye pruritus, allergic conjunctivitis, ear pain (n=1), angioedema (n=1), and non-cardiac chest pain (n=1). An overview of the ARs and classification by system organ class (SOC) are presented in Tables 3 and 4, respectively.

**Table 3: Overview of Adverse Reactions (ARs) with ORALAIR in the Safety Population (N= 307) of Children 5 through 9 Years of Age from Study 140224 (Protocol SL 74.14)**

| Endpoints | Number of events | Number of subjects | % of Safety Population |
|---|---|---|---|
| AEs suspected to be related to ORALAIR | 537 | 173 | 56.4 |
| Mild AR | 391 | 138 | 45.0 |
| Moderate AR | 131 | 66 | 21.5 |
| Severe AR | 15 | 10 | 3.3 |
| Recurrence of AR | 287 | 127 | 41.4 |
| No recurrence of AR | 250 | 106 | 34.5 |
| Dose of ORALAIR not changed | 494 | 164 | 53.4 |
| Dose of ORALAIR reduced | 5 | 2 | 0.7 |
| ORALAIR interrupted | 7 | 6 | 2.0 |
| ORALAIR discontinued | 31 | 16 | 5.2 |

Source: Adapted from Table UNP 1 (p. 1058) from Study Report Body submitted to STN 125471/230

The most common adverse reactions were associated with the system organ class (SOC) of Gastrointestinal Disorders and of Respiratory, Thoracic, Mediastinal Disorders. Most of the adverse reactions classified under both SOCs represented local application site reactions in the oropharynx. In the former SOC, these included oral pruritus (11.7%), oral paresthesia (11.1%), tongue pruritus (8.1%), mouth edema (6.2%), and lip edema (3.3%). In the latter SOC, the most common local adverse reactions included throat irritation (22.1%), cough (6.2%), and oropharyngeal pain (4.2%). See Table 4 for an overview of the adverse reactions across all SOCs.

**Table 4: Adverse Reactions by System Organ Class (SOC) with ORALAIR in 307 Children 5 through 9 Years of Age from Study 140224 (Protocol SL 74.14)**

| SOC | Severity | Number of events | Number of subjects (%) |
|---|---|---|---|
| Gastrointestinal Disorders | Mild | 192 | 98 (31.9) |
| Gastrointestinal Disorders | Moderate | 43 | 31 (10.1) |
| Gastrointestinal Disorders | Severe | 6 | 5 (1.6) |
| Respiratory, Thoracic, Mediastinal disorders | Mild | 130 | 66 (22.5) |
| Respiratory, Thoracic, Mediastinal disorders | Moderate | 48 | 34 (11.1) |
| Respiratory, Thoracic, Mediastinal disorders | Severe | 2 | 2 (0.7) |
| Eye Disorders | Mild | 18 | 17 (5.5) |
| Eye Disorders | Moderate | 14 | 12 (3.9) |
| Eye Disorders | Severe | 2 | 2 (0.7) |
| Ear and labyrinth disorders | Mild | 16 | 10 (3.3) |
| Ear and labyrinth disorders | Moderate | 9 | 9 (2.9) |
| Ear and labyrinth disorders | Severe | 1 | 1 (0.3) |
| Skin and subcutaneous tissue | Mild | 20 | 10 (3.3) |
| Skin and subcutaneous tissue | Moderate | 7 | 6 (2.0) |
| Skin and subcutaneous tissue | Severe | 1 | 1 (0.3) |
| Infections and Infestations | Mild | 3 | 3 (1.0) |
| Infections and Infestations | Moderate | 4 | 4 (1.3) |
| Infections and Infestations | Severe | 0 | 0 (0.0) |
| General disorders | Mild | 2 | 2 (0.7) |
| General disorders | Moderate | 2 | 2 (0.7) |
| General disorders | Severe | 1 | 1 (0.3) |

*Source: Adapted from Table 14.2.1-11 (starting on p.575 of 1380) from the Study Report Body submitted to 125471/230.3.*

> ***Reviewer comment:*** *Adverse reactions classified under Gastrointestinal Disorders primarily involved the oropharynx, including oral paresthesia (n=51 cases in 35 children) oral pruritus (n=42 cases in 34 children), tongue pruritus (n=34 cases in 25 children), mouth edema (n=24 cases in 20 children), and lip edema (n=10 cases in 10 children). All cases of abdominal pain (n=9 in 7 children) and vomiting (n=9 in 8 children) were mild or moderate in severity. Similarly, the predominant preferred term under Respiratory, Thoracic, and Mediastinal Disorders was also local, specifically throat irritation (n=106 cases in 70 children) and oropharyngeal pain (n=19 cases in 15 children). Thirty-one participants had adverse reactions falling under Eye Disorders, most commonly eye pruritus (n=14 cases in 14 children). The most common preferred term under Ear and Labyrinth Disorders was ear itch (n=21 cases in 16 children). These adverse reactions were very common in persons 10 through 65 years of age.*

Thirty-five of the 537 adverse reactions in this study population were assigned preferred terms associated with eosinophilic esophagitis (EoE). There were 9 cases of nausea in 3 children (1.0%), 9 cases of vomiting in 8 children (2.6%), 9 cases of abdominal pain in 7 children (2.3%), 5 cases of dysphagia in 4 children (1.3%), 2 cases of odynophagia in 2 children (0.7%), and 1 case of dyspepsia (0.3%). All cases were graded as mild or

moderate in severity Although local application site reactions were common, laryngeal edema was not reported. There was one case of mild larynx irritation.

Asthma associated with ORALAIR use was reported in three subjects, one of each for mild, moderate, and severe. The severe case was also captured as one of 2 SAEs. Other preferred terms potentially associated with asthma include cough and dyspnea. All cases of cough (n=25) in the 20 subjects were mild or moderate in severity. Of the 4 subjects with mild-to-moderate dyspnea reported on their diary cards, none of the cases were considered related to ORALAIR.

6.1.12.3 Deaths

No deaths occurred.

6.1.12.4 Nonfatal Serious Adverse Events

Two subjects experienced two SAEs that were considered "possible/likely" related to ORALAIR: (1) An 8-year-old male with grass pollen-related allergic rhinitis as well as asthma and suspected birch pollen allergy developed oral pruritus, conjunctivitis, urticaria, and asthma exacerbation within 30 minutes of his Day 5 dose of ORALAIR. Symptoms resolved with oral antihistamine and short-acting beta agonist and did not require epinephrine. The subject continued taking ORALAIR and completed the study. The verbatim term for this AR was Grade 2 anaphylaxis. (2) A 6-year-old female with grass pollen-related allergic rhinitis as well as peanut and hazelnut sensitization developed severe lip, eyelid, periorbital swelling "immediately" after ORALAIR on Day 26. No lower airway symptoms were noted. The subject recovered within 6 hours of receiving intravenous antihistamine and corticosteroid and remained stable during overnight hospitalization. ORALAIR was discontinued. The verbatim term for this AR was allergic angioedema.

> ***Reviewer comment:*** *This CBER reviewer agrees with the causality assessment of the two SAEs.*

6.1.12.5 Adverse Events of Special Interest (AESI)

Systemic allergic reactions (inclusive of anaphylaxis), laryngeal edema, and eosinophilic esophagitis are adverse events of special interest for SLIT products. There were no cases of laryngeal edema or eosinophilic esophagitis.

6.1.12.6 Dropouts and/or Discontinuations

Twenty-seven subjects (8.8%) of the 307 enrolled subjects did not complete the study. Sixteen subjects (5.2% of total population; 25% (n=4) had asthma at baseline) discontinued study participation due to AEs. Most (n=16) of the AEs leading to study discontinuation were local adverse reactions. Of these, 11 were graded as moderate (n=11, 6 requiring treatment), followed by severe (n=3) and mild (n=2). Three subjects had systemic adverse reactions.

### 6.1.13 Study Summary and Conclusions

The data from study 140244 support the safety of ORALAIR for use in children 5 through 9 years of age.

6.2 Trial #2

**V052.06**

V052.06 was a placebo-controlled, double-blinded, randomized multi-center study of ORALAIR in children 5 through 17 years of age with grass pollen-related ARC. This pre-licensure Phase 3 study was conducted in Europe from December 2006 to September 2007, and 278 persons 5 through 17 years of age with ARC were randomized 1:1 to receive either placebo (n = 139) or ORALAIR (n = 139).

The data from this pre-licensure study were reviewed during the original BLA application (STN 125471/0). The study met the pre-specified success criteria of at least a -20% point reduction in the relative difference in efficacy endpoint between ORALAIR and placebo. The study met its pre-specified primary endpoint success criterion, which was to demonstrate a reduction of at least 20% (point estimate) between the treatment and placebo arms in the average RTSS. For the intent-to-treat population, the point estimate for the difference in the average RTSS between ORALAIR and placebo groups was -25.6% (95% CI: -40.4%, -10.3%). In a post-hoc analysis, ORALAIR was demonstrated to have a -30.6% percent reduction in the daily RTSS score between treatment arm and placebo (95% CI: -47%; -14.1%); a -29.5% reduction in the daily rescue medication score (-50.9%; -8.0%); and a -30.1% reduction in the daily combined score (95% CI: -46.9%; -13.2%).. Please refer to the clinical review by Dr. Ronald Rabin for the original licensure of ORALAIR (STN 125471/230) for a detailed discussion of Study V052.06.

In response to an information request from CBER sent on June 23, 2018, Stallergenes submitted efficacy datasets and analyses for subjects 5 through 9 years of age from V052.06. To more specifically address the effectiveness of ORALAIR in the 5- through 9-year-old age group, CBER conducted *post hoc* subpopulation analyses of the efficacy data from V052.06. The point estimates and 95% confidence intervals presented in Table 5 are slightly different from the figures in the package insert because the CBER biostatistician incorporated a statistical method (i.e., delta method) to account for the uncertainty in the estimate of the average symptom score for the placebo group. This resulted in slightly different treatment effect point estimates. According to the CBER biostatistician, these small differences are likely caused by differences in numerical calculation or model fitting parameters. Please refer to the Biostatistical Review for a detailed discussion of CBER's independent analyses.

**Table 5. Percent Relative Differences with 95% Confidence Intervals for Efficacy Endpoints of Daily Combined Score (CS), Rhinoconjunctivitis Total Symptom Score (RTSS), and Rescue Medication Score (RMS) by Age Group**

| Endpoint | Age Group | Point estimate of Relative Difference (95% CI) |
|---|---|---|
| Daily CS | All | -29.5% (-47.1%, -11.9%) |
| Daily CS | 5 through 9 years old | -34.7% (-61.6%, -7.7%) |
| Daily CS | 10 through 17 years old | -24.4% (-51.6%, 2.9%) |
| Daily RTSS | All | -30.4% (-47.9%, -12.8%) |
| Daily RTSS | 5 through 9 years old | -47.1% (-75.3%, -19.0%) |
| Daily RTSS | 10 through 17 years old | -21.6% (-47.2%, 4.1%) |
| Daily RMS | All | -28.5% (-51.2%, -5.9%) |
| Daily RMS | 5 through 9 years old | -26.5% (-60.2%, 7.1%) |
| Daily RMS | 10 through 17 years old | -28.3% (-70.1%, 13.5%) |

Source: Table 9 from the Biostatistical Review by Jennifer Kirk, who derived these data from V052.06 ef_dd dataset

> ***Reviewer comment:*** *This study was not designed to demonstrate the effectiveness of ORALAIR in different pediatric age subgroups. The post-hoc analysis was performed to evaluate the efficacy trend in 5 through 9-year-olds. These data do not raise concerns regarding the effectiveness of ORALAIR in children 5 through 9 years of age. Although these data are limited, the slightly increased point estimates for efficacy appear to be consistent across the efficacy endpoints shown.*

In conclusion, Study V052.06 demonstrated efficacy of ORALAIR in children and adolescents 5 through 17 years of age, and a post-hoc subpopulation analysis of efficacy in the 5- to 9-year-old age group showed similar efficacy compared to the overall study population.

## 9. Additional Clinical Issues

### 9.1.1 Human Reproduction and Pregnancy Data

Stallergenes reported that a total of 28 pregnancies (13 in ORALAIR, 15 in placebo) occurred across three studies conducted in adults (V034.04, V053.06, and V061.08USA), with 25 having known outcomes. Abnormal outcomes in two ORALAIR recipients include a spontaneous abortion and neonatal ventricular septal defect. There was 1 fetal death (premature delivery due to chorioamnionitis) and extrauterine pregnancy in 2 placebo recipients. Two elective abortions occurred, one in each study arm. These data were not sufficient to determine the presence of absence of ORALAIR-associated risks, and this was conveyed in Section 8.1 of the package insert.

### 9.1.2 Use During Lactation

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

### 9.1.3 Pediatric Use and PREA Considerations

With this submission, Stallergenes has fulfilled the post-marketing requirement to conduct a pediatric study evaluating the safety of ORALAIR in children 5 through 9

years of age. A partial waiver for evaluating ORALAIR in subjects younger than 5 years of age is granted on the basis that necessary studies were deemed impossible or highly impracticable because the number of children younger than 5 years of age with grass pollen-related ARC is too small.

### 9.1.4 Immunocompromised Patients

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

### 9.1.5 Geriatric Use

The safety and effectiveness of ORALAIR have not been established in persons over 65 years of age.

## 10. CONCLUSIONS

ORALAIR is safe and effective in the treatment of grass pollen-related allergic rhinitis with or without conjunctivitis in children 5 through 9 years of age.

## 11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS11.1 RISK-BENEFIT CONSIDERATIONS

Data from study V052.06, a Phase 3 double-blinded, randomized, placebo-controlled study evaluating the effectiveness of ORALAIR, establish that ORALAIR decreases symptoms of grass pollen-related rhinoconjunctivitis in children 5 through 17 years of age who have been confirmed to have a positive skin test or pollen specific IgE antibodies to any of the 5 grass species contained in the product. The safety data submitted to this supplement suggest that the 307 children 5 through 9 years of age enrolled in Study 140244 tolerated ORALAIR for 30 days with mild or moderate adverse reactions due to local application reactions such as throat irritation, oral pruritus, oral paresthesia, tongue pruritus, mouth edema, cough, ear pruritus, oropharyngeal pain, eye pruritus, lip edema, vomiting, tongue edema, abdominal pain, oral discomfort, tongue edema and allergic conjunctivitis. There were two serious adverse events (SAE), anaphylaxis and angioedema, both of which were characterized as "probable/likely" due to ORALAIR. There were no deaths. These data supplement an existing safety database from placebo-controlled clinical trials in 154 children 5 through 17 years of age of whom 147 were exposed for more than 3 months. Taken together, these data support a favorable benefit-risk assessment for use of ORALAIR in children 5 through 9 years of age.

### 11.3 Discussion of Regulatory Options

Although Study 140244 had limitations due to the open-label study design and descriptive analyses, these data in a pediatric age subgroup of children 5 through 9 years of age supplement an existing safety database with the product. The safety profile of ORALAIR was established in 1038 adults 18 through 65 years of age in 6 placebo-controlled clinical trials and 154 children 5 through 17 years of age. In addition, ORALAIR has been licensed in the U.S. for use in persons 10 through 65 years since

2014 and the safety of ORALAIR has been evaluated in 1728 persons (920 of which were children 5 through 17 years of age) in post-marketing studies. These data are described in the currently approved package insert for ORALAIR, and the safety data submitted in this BLA supplement are consistent with the safety data described in the package insert. Thus, the available safety and effectiveness data are sufficient to support approval of ORALAIR for use in children 5 through 9 years of age.

11.4 Recommendations on Regulatory Actions

The data submitted to this supplemental BLA support licensure of ORALAIR in children 5 through 9 years of age.

11.5 Labeling Review and Recommendations

CBER and Stallergenes reached concurrence on the revised package insert for ORALAIR. The Indications and Usage section of the package insert was revised to indicate that the product is approved for use in persons 5 through 65 years of age. Section 6 was revised to include data from Study 140244, which supported safety in children 5 through 9 years of age. As required, Stallergenes revised Section 8 in accordance with the Pregnancy and Lactation Labeling Rule (PLLR).

11.6 Recommendations on Postmarketing Actions

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