

Summary Basis for Regulatory Action Template

Date: March 31, 2014

From: Jennifer L. Bridgewater, MPH, Chair of the Review Committee

BLA/ STN#: 125471

Applicant Name: Stallergenes, S.A.

Date of Submission: December 18, 2012

Review Goal Date: April 1, 2014

Proprietary Name: ORALAIR®

Established Name: Sweet Vernal, Orchard, Perennial Rye, Timothy, and Kentucky Blue Grass Mixed Pollens Allergen Extract

Indication:

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 vitro testing for pollen-specific IgE antibodies for any of the five grass species included in this product. ORALAIR is approved for use in persons 10 to 65 years of age.

Dosage Form: Tablet for Sublingual Use

Recommended Action: Approval

Signatory Authorities Action:

Offices Signatory Authority: Marion F. Gruber, Director, Office of Vaccines Research and Review

☒ **I concur with the summary review.**

☐ **I concur with the summary review and include a separate review to add further analysis.**

☐ **I do not concur with the summary review and include a separate review.**

Specific documentation used in developing the SBRA	Reviewer Name –Date of Review
Clinical Review	Ronald L. Rabin, M.D. – March 21, 2014
Pharmacovigilance Plan Review	Patricia Rohan, M.D.- June 10, 2013
Statistical Review	Tammy Massie, Ph.D. – February 12, 2014
CMC Review	Taruna Khurana, Ph.D.- March 19, 2014
Microbiological Methods Validation Review	Hyesuk Kong, Ph.D.- July 23, 2013
Toxicology Review	Ching Long Joseph Sun, Ph.D.- December 12, 2013
Bioresearch Monitoring Review	Dennis T. Cato – June 24, 2013 August 14, 2013
Facilities Review and Establishment Inspection Report	Richard Heath Coats – March 26, 2014
Proprietary Name	Kristine T. Khuc, Pharm.D. – March 19, 2013 January 14, 2014
Advertising and Promotional Labeling	Kristine T. Khuc, Pharm.D. – July 13, 2013
Approved Draft Labeling	N/A (date when final draft labeling was approved)
Advisory Committee Transcript	December 11, 2013

1. Introduction

Stallergenes S.A. submitted a Biologics License Application (BLA) 125371 for licensure of Sweet Vernal, Orchard, Perennial Rye, Timothy, and Kentucky Blue Grass Mixed Pollens Allergen Extract. The proposed proprietary name for this product is ORALAIR, and the dosage form for this product is a tablet for sublingual use. ORALAIR is indicated for immunotherapy 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 any of the five grass species included in this product for use in persons 10 to 65 years of age.

ORALAIR is a freeze-dried tablet formulation of a mixed grass pollen extract for sublingual use. ORALAIR tablets are to be placed under the tongue until dissolution. ORALAIR is the first approved allergen extract in the U.S. for sublingual immunotherapy (SLIT). ORALAIR is for immunotherapy use only and is not approved for diagnostic use. ORALAIR tablets are presented in labeled blister packages containing single doses for patient self-administration. Labeling includes a Black Box warning and a medication guide, both of which emphasize the potential risk for severe allergic reactions and a need for access to auto injectable epinephrine.

Among the CMC review issues that arose and were resolved during the review were cleaning validation, validation of the mixing process, validation of the firm's --(b)(4)-- method per CBER procedures in order to assess potency in BAUs, and stability data for the final drug product.

Clinical issues that arose were the size of the safety database for pediatric patients 5 – 9 years of age and concerns about anaphylactic reactions due to the product. These were resolved by restricting the product indication to persons 10 – 65 years of age and recommendations for availability of auto injectable epinephrine during treatment.

2. Background

Product Description

ORALAIR is a round, biconvex, slightly speckled white to beige tablet for sublingual use. Tablets are engraved with '100' or '300' on each side, depending on dose strength. ORALAIR sublingual tablets are provided in aluminum/aluminum blister packs in two dose strengths, 100 IR and 300 IR. The 100 IR tablets are provided in a starter pack for children and adolescents (persons 10 – 17 years of age) containing 3 blister packaged tablets. The 300 IR tablets are also provided in a starter pack for adults containing 3 tablets and in a sample pack for children and adolescents and adults containing 30 blister packaged tablets.

The Index of Reactivity (IR) is the biological potency unit used by the applicant in the clinical studies provided in the BLA and is defined as follows:

The titer of an allergen extract corresponds to 100 IR/mL when, in a skin prick test performed with the Stallergenes' skin prick test device (i.e., the Stallerpoint®), in 30 subjects sensitized to the allergen in question, the extract produces a wheal measuring 7 mm in diameter (geometric mean). Skin reactivity in these subjects is simultaneously demonstrated by a positive response to a prick-test with 9% codeine phosphate or 10 mg/mL histamine dihydrochloride.

For routine product manufacturing, the IR is determined by an -----(b)(4)----- method. In addition to the IR potency units, the tablets are also tested for Bioequivalent Allergy Units (BAUs), a CBER measurement of potency for grass pollens present in this product. For ORALAIR, the CBER grass reference used is Timothy grass pollen. The corresponding BAU values and ranges to the IR values of the tablets are as follows:

- 100 IR = 3000 BAU (range ----(b)(4)---- BAUs)
- 300 IR = 9000 BAU (range -----(b)(4)----- BAUs)

Regulatory History

Allergic rhinoconjunctivitis (ARC) affects over 500 million persons worldwide, including approximately 30 million persons in the US. While allergen avoidance and pharmacotherapy can provide significant relief, for many affected individuals symptoms remain. For some of these patients, allergen immunotherapy is a reasonable therapeutic alternative. Subcutaneous allergen immunotherapy (SCIT) has been practiced since the early 20th century; the administration of

allergen extracts orally or sublingually (SLIT) is a more recent development, increasing in popularity in Europe and the U.S. However, U.S. licensed allergen extracts for pollens, mold spores, animal danders, insects and inhalants are only approved for use in SCIT. ORALAIR is the first approved allergen extract in the U.S. for SLIT.

Stallergenes S.A. submitted a Biologics License Application (BLA) for a 5-grass pollen extract tablet for sublingual administration on December 18, 2012. The established name for this product is Sweet Vernal, Orchard, Perennial Rye Timothy, and Kentucky Blue Grass Mixed Pollens Allergen Extract and the approved trade name for this product is ORALAIR.

Stallergenes S.A. evaluated ORALAIR under U.S. IND 13776. The BLA includes one clinical study conducted in the U.S. under this IND and five studies conducted in Europe (not under IND). Most of the available clinical data are from Europe, because ORALAIR has been licensed in the EU since 2008. Several meetings and discussions were held with the applicant under the IND to resolve issues such as optimal dosage, endpoint parameter for assessing proof of efficacy and statistical differences between treatment and placebo groups required to meet proof of efficacy.

During the IND review process and prior to submission of this BLA; potential issues related to defining clinical efficacy of future Allergenic Products were discussed with the Allergenic Products Advisory Committee (APAC) on May 12, 2011. Specifically, FDA discussed with the APAC the potential use of Environmental Exposure Chambers (EEC's) to assess efficacy in clinical studies. EECs are self-contained units with controlled air that expose patients to specific and quantifiable amounts of allergens, such as pollens. The FDA provided background information on the advantages and disadvantages of natural exposure studies for seasonal allergens and the potential use of Environmental Exposure Chambers (EECs) to better control for variability. The APAC discussed the challenges of designing a controlled environmental study of sufficient size, as well as a natural exposure study during a low pollen season in which the difference in clinical endpoints between the placebo and treatment groups could be small. The APAC stated there was not as much experience with EEC challenges versus natural exposure to determine their relative utility in establishing efficacy. However, EECs may be more useful as an adjunct to natural exposure clinical trials. Stallergenes performed one Phase 2 study in the EU using an EEC to assess safety and efficacy of the product in adult subjects.

Also discussed at this APAC meeting in 2011 were Statistical Considerations for the Design and Interpretation of Phase III Clinical Trials of Allergenic Products. FDA presented an overview of statistical concepts applied in the review of Phase 3 studies of allergenic products. Discussions included covariates, clinically meaningful differences, and the appropriate timeframes for performing studies with respect to allergy seasons. A particular concept from the APAC discussion applicable to the clinical study data submitted to this BLA is that the lower bound of the 95-percent confidence interval between the treatment and control group should be greater than a pre-specified threshold to ensure that a statistical significance difference translates into a clinically meaningful difference.

3. Chemistry Manufacturing and Controls (CMC)

a) Product Quality

Product Composition

The composition of the ORALAIR final Drug Product (DP) tablets and the function of the ingredients in the DP tablets are provided in Table 1 below.

Table 1 – Composition of ORALAIR Final DP Tablets

NAME OF INGREDIENTS	FUNCTION	QUANTITY PER TABLET
5-grass pollen allergenic extract ((b)(4) freeze-dried) – Active Ingredient	Drug substance	Quantity equivalent to 100 IR* or 300 IR*
Microcrystalline cellulose – Excipient	--(b)(4)--	--(b)(4)--
Croscarmellose sodium – Excipient	--(b)(4)--	--(b)(4)--
Colloidal anhydrous silica – Excipient	--(b)(4)--	--(b)(4)--
Magnesium stearate - Excipient	--(b)(4)--	--(b)(4)--
Lactose monohydrate – Excipient	--(b)(4)--	----(b)(4)----

* The quantity of drug substance is calculated according to the total allergenic activity (IR/mg) of the involved batch(es) of drug substance.

** The quantity of Lactose monohydrate needed is calculated against the quantities of drug substance and other excipients, to reach a total mass of (b)(4) per tablet.

Presentation and Packaging System

Manufacturing Overview

Acceptance ranges and specifications for the DS were determined based on process validation and comparability studies. In order to maintain consistency in the DS manufacturing process, various in-process measurements are in place such as -----
----- (b)(4) -----

Throughout the process development DS quality was monitored by measuring parameters that could have been affected by the process changes.

The specifications for the ORALAIR DS at release and at end of shelf life (36 months) are indicated in Table 2 below.

Table 2 – ORALAIR Drug Substance Specifications

(b)(4)

Stability studies were performed in support of the storage time for the DS and to confirm the appropriate specifications for the DS throughout the expiry period. The DS is -----
----- (b)(4) ----- The dating period of the DS is --- (b)(4) ---
when stored at ----- (b)(4) -----.

The applicant performed process development, analytical methods development and stability studies to establish the suitability of their DS. The specific release criteria developed for the DS are suitable to demonstrate suitability for intended use.

Drug Product

The ORALAIR (DP) is a solid, single-dose tablet preparation for sublingual administration. The DP tablet is prepared by -----(b)(4)----- . The DP is manufactured by two contract tableting firms; -----(b)(4)-----.

Manufacturing of the DP includes weighing of materials, pre-mixing, mixing, ---(b)(4)---, tablet compression, and packaging. The first step, weighing of materials (DS active ingredient and excipients) is important as this step defines the date of manufacture.

Validation of the mixing process was a primary CMC review issue that was resolved during the review. The applicant agreed that mixing would be identified as a -----(b)(4)----- step and would establish appropriate specifications and limits. In addition, the applicant will perform a revalidation of the mixing process at the ---(b)(4)--- contract drug facility during the next manufacturing campaign.

The DP manufacturing process was originally performed at (b)(4) (formerly known as -----(b)(4)---). During the development process prior to the BLA submission, Stallergenes S.A. determined an additional contract DP manufacturing site was required to expand the number of tablets produced. An additional contract facility, -----(b)(4)-----, was therefore added approximately a year after (b)(4). Comparability studies were performed to demonstrate that the quality of DP produced between the two sites was similar.

The DP validation was performed as per cGMP requirements and relevant FDA and ICH guidelines. Three full scale batches manufactured at -----(b)(4)----- were used during process validation studies. As the two sites use some different equipment and apply different ranges of controlled parameters, the equipment were qualified for their intended use prior to process validation. Final specifications for the ORALAIR 100 and 300 IR DP tablets are identical with the exception of total allergenic activity, and are as follows:

Table 3 – Drug Product Specifications

TESTS	METHODS	SPECIFICATIONS AT RELEASE	SPECIFICATIONS AT SHELF LIFE
Macroscopic appearance	Visual inspection	Round and biconvex, white to beige, slightly speckled tablets, engraved 300 on each side	Round and biconvex, white to beige, slightly speckled tablets, engraved 300 on each side
Protein profile	---(b)(4)---	----- ----- ----- -----	----- ----- ----- -----
Disintegration test	----- (b)(4) ----- -----	(b)(4)	(b)(4)
Leakage test on blister Packs	----- (b)(4) -----	No abnormality	No abnormality

final DP tablets in IR Units; CBER also required the applicant to measure the potency in BAUs. During review of the BLA, the applicant validated the CBER -----(b)(4)----- method in accordance with CBER method and optimization protocols in order to measure potency in BAUs. This issue was resolved and the applicant will provide BAU values in addition to their standard potency measurement of IR.

Regarding cleaning validation, DMPQ noted during the facilities review and inspectional process that there were concerns about effective cleaning validation studies for processing equipment associated with both DS and DP manufacture. Both the applicant and one of the applicant's contract manufacturers of final drug product (--(b)(4)--) received inspectional observations for inadequate or incomplete cleaning validation studies. Of particular concern was cleaning validation of shared manufacturing equipment. Both firms re-executed their cleaning validation studies to resolve DMPQ's concerns and address inspectional observations.

Post-Marketing Studies Not Subject to Reporting Requirements of 21 CFR 601.70

1. To continue testing stability of Drug Substance batches -----(b)(4)----- through the ----- (b)(4)----- time points and to submit these data for review in the form of Post Marketing Commitment Submissions in October, 2014; October, 2015; and August, 2016.
2. To perform a revalidation of the mixing process at the -----(b)(4)----- contract drug product manufacturing site during the next manufacturing campaign with a target RSD for total allergenic activity of less than or equal to (b)(4). The data from this revalidation study will be submitted to CBER for review in the form of a Post Marketing Commitment Submission in April, 2015.

b) CBER Lot Release

The lot release protocol template (LRP) for the final filled product was submitted to CBER for review and found acceptable after revisions. Samples from seven lots of the 100 IR and 300 IR formulations were submitted for lot release testing and were found to be acceptable. Lot numbers submitted were: 378-2, 379-1, 380-1, 381-1, 382-1, 121-1 and 378-1.

The applicant and CBER agreed that only the final blister packaged tablet drug product will be released by CBER. For routine lot release, the firm will submit samples and a LRP for each final DP blister pack lots to CBER. A lot testing plan was developed by DBPAP, DMPQ and DBSQC and was found acceptable.

c) Facilities review/inspection

The following facilities are involved in the manufacture of ORALAIR.

Drug Substance

STALLERGENES S.A.
6 rue Alexis de Tocqueville
92183 Antony Cedex FRANCE

FEI 3004015717

Manufacturing, packaging, labelling, testing and final batch release of the drug substance and stability testing of the drug substance is performed at this site. A Pre-License inspection of this facility was performed June 26– July 2, 2013, and the inspection was designated Voluntary Action Indicated (VAI). The compliance status of this site is deemed acceptable for product approval.

Contract Drug Product Filling Sites

----- (b)(4) -----

Control of excipients and packaging, manufacture of the final drug product tablets, primary and secondary packaging, release testing, and stability testing according to a formal stability program are performed at this site. A Pre-License inspection of this facility was performed ----- (b)(4) -----, and the inspection was designated Voluntary Action Indicated (VAI). The compliance status of this site is deemed acceptable for product approval.

----- (b)(4) -----

Control of excipients and packaging, manufacture of the final drug product tablets, primary and secondary packaging, release testing, and stability testing according to a formal stability program are performed at this site. ----- (b)(4) -----, a multi-product facility was inspected by FDA's International Operations Group, ----- (b)(4) -----, and was classified VAI. Based on the information provided in the BLA submission and the previous inspection reports supporting the overall compliance status of the contract manufacturing facility, inspection of this facility in support of the ORALAIR BLA was waived.

d) Environmental Assessment

The applicant included a request for a Categorical Exclusion to omit preparation of an Environmental Assessment, under 21 CFR Part 25.31(c) in the original BLA STN 125471/0 for 5-grass pollen extract (ORALAIR). Based on the information submitted and the nature of this product, the sponsor's request for Categorical Exclusion from an Environmental Assessment under 21 CFR 25.31(c) is justified. This product is composed of naturally occurring substances and manufacturing of this product will not alter significantly the concentration and distribution of the natural substance, its metabolites, or degradation products in the environment, and no

extraordinary circumstances exist that might cause this action to have a significant effect on the quality of the human environment.

4. Nonclinical Pharmacology/Toxicology

Non-clinical toxicity studies were conducted in order to identify and evaluate any toxicity findings following the administration of ORALAIR. These included two relevant GLP-compliant toxicity studies administered orally in a 13-week cheek pouch local tolerance study in hamsters and a 26-week oral gavage toxicity study in rats. Treatment of female hamsters for 13 weeks caused slightly higher incidence of acanthosis in the left bottom of the cheek pouch. The local effect can be monitored clinically and is not considered adverse. Oral treatment of rats for 26 weeks did not reveal any significant safety issues.

Two reproductive toxicity studies performed in female rats and rabbits to evaluate the effect of the product on embryo-fetal development revealed no evidence of harm to the fetuses due to ORALAIR. Specifically, there were no product-related fetal malformations or other evidence of teratogenesis observed in rabbits and rats at doses up to 1000 IR/kg/day, which is equivalent to 200 times the recommended maximum adult dose of 300 IR or 5 IR/kg/day on a typical adult body weight of 60 kg. Based on the data derived from these studies ORALAIR received a pregnancy Category B designation which will be reflected in Section 8.1: *Pregnancy* of the ORALAIR PI.

A study to evaluate the effect of ORALAIR on male fertility was not conducted.

ORALAIR did not cause any mutagenic or clastogenic activity in the *in vitro* bacterial mutagenesis assay and mouse lymphoma assay or the *in vivo* bone marrow micronucleus and unscheduled DNA synthesis test in rats.

5. Clinical Pharmacology

The mechanisms of action of allergen immunotherapy are not known.

6. Clinical/Statistical

Overview

The BLA contains data from six clinical studies. Five of these studies support efficacy for U.S. licensure of ORALAIR. These include a pivotal Phase 3 "natural field" clinical trial (VO61.08) conducted in the U.S. under IND 13776 and four additional studies, all of which were conducted in Europe, and were not under U.S. IND (VO34.04, VO52.06, VO53.06 were natural field studies and VO56.07 was an environmental chamber study). These studies were conducted over several years and used a number of scoring algorithms for allergic rhinoconjunctivitis (ARC) symptoms, medication use for relief of symptoms, and combinations of symptoms and medication use as clinical endpoints for evaluation of efficacy. Daily symptoms and medication

use were self-assessed and recorded by subjects and collected during Study Visits. One or more of the scoring algorithms defined below were used as primary efficacy endpoints in each of these studies.

Rhinoconjunctivitis Total Symptom Score (RTSS): the total of six symptom scores (i.e., sneezing, rhinorrhea, nasal pruritus, nasal congestion, ocular pruritus, and watery eyes). Each score ranges from 0 to 3 (absent, mild, moderate, severe); the maximum RTSS is 18.

Average Rhinoconjunctivitis Total Symptom Score (ARTSS) is the RTSS averaged over the duration for a pollen season for a given subject.

The daily *Rescue Medication Score (RMS)* is a score that accounts for the use of allowed rescue medication by subjects in natural field studies based on the following scale that assumes increasing effectiveness among medication types: 0=absent, 1=antihistamine, 2=nasal corticosteroid, 3=oral corticosteroid.

The daily *Combined Score (CS)* is the arithmetic mean of the RTSS and RMS and thus gives equal weight to symptoms and medication use. The CS ranges from 0 to 3.

The daily *Adjusted Symptom Score (ASS)* is an algorithm of symptom score that takes into account use of rescue medication for each day reported on the daily diary card as well as a contribution to the score based on the prior day's rescue medication use because of the potential for residual effect from rescue medication. The ASS ranges from 0 to 18 (Grouin et al, 2011).

Average Adjusted Symptom Score (AASS) is the average of the daily Adjusted Symptom Score over the evaluation period.

For the natural field trials, CBER preferred combined symptom and medication scores as the most accurate measure of efficacy because combined scores account for variability among study subjects' ability to tolerate symptoms without taking medication. Of the two algorithms for combining symptom and medication scores, CBER preferred the CS because its calculation is relatively straightforward. Therefore, CBER requested post-hoc analyses of some of the European studies to calculate the point estimate difference and 95% CI of the CS. CBER's pre-specified criteria based on the Intent To Treat (ITT) study population for efficacy to support US licensure included a point estimate difference between treatment and placebo of -15% and an upper bound of the 95% CI of that difference of $\leq -10\%$.

The five studies provided in the BLA to support U.S. licensure are summarized below.

VO61.08 USA (Pivotal U.S. efficacy study in adults):

This Phase 3 study was conducted in the U.S. in 2009. A total of 473 adults 18 through 65 years of age with ARC were randomized 1:1 to either placebo (n = 240) or ORALAIR (300 IR, n = 233) for four months prior to the onset of, and throughout the grass pollen season. The primary objective was to assess the safety and efficacy of ORALAIR 300 IR during the grass pollen season. The primary efficacy endpoint parameter was the CS. The percent change in the CS was

-28.2% (95% CI -43.3%, -13.0%) in the ORALAIR 300 IR group compared to the placebo group. These data met CBER's criteria for success.

VO52.06 EU (European study in children and adolescents):

This Phase 3 study was conducted in Europe from December 2006 to September 2007. A total of 278 persons 5 through 17 years of age with ARC 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 ORALAIR group was dosed 100 IR on Day 1, 200 IR on Day 2, and 300 IR on each day thereafter. The primary objective was to assess the safety and efficacy of ORALAIR 300 IR during the grass pollen season. The primary efficacy endpoint parameter was the ARTSS. However, CBER requested post-hoc analysis of the CS. The percent change in the CS was -30.1% (95% CI -46.9%, -13.2%) in the ORALAIR 300 IR group compared to the placebo group. These data met CBER's criteria for success.

VO56.07 EU (Environmental exposure chamber study in adults)

This study was conducted in Europe from September 2007 to March 2008. A total of 89 subjects 18 through 50 years of age with ARC and a pre-treatment RTSS score of >7 after allergen challenge in an Environmental Exposure Chamber (EEC) were randomized 1:1 to receive either placebo (n = 44) or ORALAIR 300 IR (n = 45) for four months. After initiating treatment, subjects were exposed to allergen in an EEC on four occasions: Week 1, and Months 1, 2, and 4. The primary objective of this study was to assess the efficacy of ORALAIR 300 IR during the Month 4 EEC challenge. The primary efficacy endpoint parameter was the ARTSS (medications are not used in the EEC). The percent change in the ARTSS was -28.8% (95% CI -43.7%, -13.7%) in the ORALAIR 300 IR group compared to the placebo group. These data met CBER's criteria for success.

VO53.06 (Five year study in adults to evaluate effectiveness after three seasons of treatment)

This Phase 3 study was conducted in Europe from December 2006 - September 2011. A total of 663 subjects 18 through 50 years of age with ARC were randomized 1:1:1 to one of three groups: placebo (n = 219), ORALAIR 300 IR four months prior to the onset of the grass pollen season (n = 207) or ORALAIR 300 IR two months prior to the onset of the grass pollen season (n = 207). All subjects were treated prior to and throughout three consecutive grass pollen seasons, for a total of ~20-24 weeks per year. The primary objective was to assess the efficacy of ORALAIR on the AASS during the third pollen season and during the two years of post-treatment observation. However, CBER requested post-hoc analysis of the CS. During the third pollen season, percent change in the CS for subjects in the 4 month ORALAIR 300 IR pre-treatment group was -40.9% (95% CI -57.4%, -24.5%) compared to placebo. These data met CBER's criteria for success. In Years 4 and 5, during which treatment was discontinued, the 95% CI Upper Limit was -6.0% and +0.3% respectively. Years 4 and 5, therefore, did not meet CBER's criteria for success.

VO34.04 EU (Dose selection study)

This study was conducted in Europe in 2005. A total of 628 adults 18 through 45 years of age with ARC were randomized 1:1:1:1 to receive placebo (n = 156) or one of three doses of study drug, 100 IR (n = 157), 300 IR (n = 155) or 500 IR (n = 160), for four months prior to the onset of, and throughout the grass pollen season. While the primary objective was to assess the

efficacy of sublingual immunotherapy on the ARTSS during the grass pollen season, CBER focused on the post-hoc analysis of the CS. The percent change in the CS was -30% (95% CI -43, -16%) in the ORALAIR 300 IR group compared to placebo. These data met CBER's criteria for success.

In addition, Study VO60.08 was included in the BLA. This study was conducted in Europe from February 2009 through August 2009, and included a total of 381 subjects 12 through 65 years of age who were randomized 1:1 to placebo or ORALAIR 300 IR. The primary efficacy endpoint parameter was the AASS. There were no statistically significant differences between each of the treatment groups and placebo, and this study therefore did not support efficacy of ORALAIR.

Summary of Clinical Efficacy

Across four of the five natural field studies, subjects treated with ORALAIR 300 IR for four months prior to the grass pollen season and during the pollen season experienced a reduction in clinical score (either symptom score or a combined symptom and medication score). The EEC study supported the natural field studies. The totality of the data are consistent with CBER's criteria for success of a point estimate difference in the CS between treatment and placebo groups of -15% or better, and a 95% CI upper limit of -10% or better. Therefore, CBER considers ORALAIR to be effective for the treatment of ARC by immunotherapy for any of the five grass species included in this product in persons 10 to 65 years of age.

In the clinical studies, there were no significant differences in efficacy among males and females. In addition, the percent change in the CS in the ORALAIR 300 IR group compared to placebo observed in the pediatric trial (VO52.06; -30.1%) is within the range of that observed in the US pivotal trial for adults (VO61.08; -28.2%). These data suggest that ORALAIR is similarly efficacious for children and adolescents as for adults.

There were also no differences in efficacy among subjects who were mono-sensitized (defined as sensitive only to the group of five-grass pollen allergens) or those who were "poly-sensitized" (also sensitive other environmental allergens). However, there are regional and individual differences regarding the impact of polysensitization on grass pollen-induced ARC. Depending on region, tree pollen season may overlap with the beginning of grass pollen season, and ragweed pollen season may overlap with the end of grass pollen season. To avoid the confounding effect of multiple allergen exposure, polysensitive subjects who are exposed to additional allergens during grass pollen season were excluded from the clinical studies. For example, subjects who were sensitive to both tree and grass pollens and who live in a region in which these two pollen seasons overlap were excluded from the study. Consequently, polysensitive patients who are exposed to additional allergens during grass pollen season may not benefit from ORALAIR treatment to the same degree as the polysensitive subjects in these clinical studies, who were not exposed to any other allergens during grass pollen season.

There were also no differences in efficacy between subjects with and without asthma. However, only subjects with mild asthma requiring intermittent rescue medication were included in the clinical studies. Therefore, patients with asthma that requires daily therapy may not benefit from ORALAIR to the same degree as the asthmatic subjects who participated in these clinical studies.

Bioresearch Monitoring Review

Three domestic sites and one foreign site were inspected under the agency's Bioresearch Monitoring program. The inspection reports for all four sites were received and reviewed, and did not reveal problems that impacted the data submitted in the BLA.

Pediatric Research Equity Act (PREA)

Under PREA (21 U.S.C, 355c), this application is 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 26, 2014, with a request for a partial waiver from the requirements of PREA for children from birth to <5 years of age, and a deferral for studies in children 5 to < 10 years of age. On March 19, 2014, the applicant's pediatric plan was presented to the Pediatric Review Committee (PeRC), who agreed with CBER's decision to grant the following:

- The pediatric study requirement in children from birth to 5 years of age for the proposed indication is waived.
- Submission of the pediatric study in children ages 5 to <10 years in this application is deferred.

The applicant agreed to the following dates for the PREA required deferred pediatric study for immunotherapy for the treatment of diagnosed grass-pollen induced allergic rhinitis with or without conjunctivitis, in children 5 to 9 years of age:

Final Protocol Submission Date: 6/30/2014

Study Start Date, First Patient Visit by: 02/01/2015

Study Completion Date: 06/30/2016

Clinical Study Report Submission Date: 12/31/2016

7. Safety

Overview

Safety data from six clinical trials of ORALAIR are provided in the BLA for a total of 1514 subjects who received ORALAIR at any dose. The six clinical trials include the five trials outlined above and VO60.08, a study of adults that failed to demonstrate efficacy. From these studies, 1,038 adults and 154 children and adolescents received ORALAIR 300 IR. There were 840 adult placebo subjects, and 158 placebo subjects who were children or adolescents. While only the 300 IR dose was evaluated for overall safety, CBER did note AE associated with the 500 IR dose as potential safety signals that might be applied to the 300 IR dose.

Adults

In the adult pooled analysis, several treatment-emergent adverse events (TEAE) were reported at a higher frequency following ORALAIR than placebo. The most commonly reported TEAE were oral pruritus (32.6% ORALAIR; 6.6% placebo) and throat irritation (21.1% ORALAIR; 3.8% placebo). Other TEAEs reported in >2.5% of ORALAIR recipients and at a higher frequency than placebo recipients included tongue and ear pruritus, edema of the mouth, lip, tongue, or pharynx, oral paresthesia, and dyspepsia.

Among adults, 4.7% (49/1038) of ORALAIR recipients and 1.1% (9/840) of placebo recipients withdrew from studies due to a TEAE. TEAE leading to study withdrawal in 2 or more (range 2-5) adults who received ORALAIR were oral pruritus, upper abdominal pain, vomiting, mouth, tongue and pharyngeal edema, dyspepsia, dysphagia, throat irritation, and chest discomfort.

At least one serious adverse event (SAE) was reported in 13 (1.3%) of ORALAIR recipients and 5 (0.6%) of placebo recipients. Of these, one SAE was “possibly related” to ORALAIR--an episode of gastroenteritis in a 43 year old female that began 93 days after initiating ORALAIR. She was hospitalized and treated with antibiotics. The subject recovered from the gastroenteritis within approximately one week and discontinued ORALAIR and withdrew from the study.

There were also two reports of SAE that were severe laryngopharyngeal disorders that were considered certainly related to ORALAIR:

- A 30-year-old male experienced severe laryngeal edema and redness of the face within 5 minutes of receiving the first dose of ORALAIR. He received intravenous prednisolone. The event resolved within 30 minutes. He discontinued ORALAIR and withdrew from the study.
- A 25-year-old female experienced severe hypersensitivity, beginning 5 minutes after receiving the first dose of ORALAIR. Symptoms included violent coughing and marked dyspnea. She received antihistamines, salbutamol and prednisolone, and recovered by Day 3.

There were no cases of anaphylactic shock or use of epinephrine in the clinical studies. There were no deaths reported in study participants.

Children and Adolescents

The pediatric safety data base includes all children and adolescents 5-17 years of age who participated in the European pediatric study VO52.06, and children 12-17 years of age who participated in Study VO60.08, a European study of subjects 12-65 years of age. Together, there were 154 ORALAIR recipients, and 158 placebo recipients. Approximately 45% of subjects were 5-11 years of age. Approximately 33% had mild asthma. Several TEAEs were reported at a higher frequency following ORALAIR than placebo including oral pruritus (33.1% ORALAIR; 4.3% placebo), mouth edema (12.9% ORALAIR; 0.0% placebo), and throat irritation (9.4% ORALAIR; 5.0% placebo). Other TEAEs reported in >2.5% of ORALAIR recipients included tongue, lip, and ear pruritus, lip and tongue edema, upper abdominal pain, and vomiting.

Among all children and adolescents, 5.2% (8/154) of ORALAIR recipients and 1.3% (2/158) of placebo recipients withdrew from study participation due to TEAE; including oral pruritus, mouth edema, vomiting, chest discomfort, and oropharyngeal blistering.

At least one serious TEAE was reported in 1 (0.6%) recipient receiving ORALAIR and 2 (1.3%) recipients receiving placebo. None of these serious TEAE's was considered by the investigator to be related to the study product. No cases of anaphylaxis, use of epinephrine, or of severe laryngopharyngeal disorders were reported in children or adolescents; there were no deaths.

Summary of Clinical Safety

Based on the safety data ORALAIR at 300 IR per dose appears to be safe and effective for immunotherapy of ARC for any of the five grass species included in this product in persons 10 to 65 years of age. CBER considers ORALAIR to be safe for the treatment of ARC for any of the five grass species included in this product in persons 10 to 65 years of age.

Because the small diameter of the upper airway of younger children may be more easily occluded during a laryngopharyngeal allergic reaction, and because of the low number of young children who have been studied in the pediatric clinical trial with ORALAIR, CBER has limited the indication of ORALAIR to children 10-17 years of age. The indication for children 5-9 years of age will be re-evaluated upon completion of safety studies in these children, as mandated by PREA.

8. Advisory Committee Meeting

The Allergenic Products Advisory Committee (APAC) convened on December 11, 2013, to hear presentations by CBER and the applicant on the safety and efficacy of ORALAIR. Ten voting members were in attendance. The following questions were presented to the committee:

1. Do the available data support the efficacy of Oralair for the treatment of grass pollen-induced allergic rhinitis or conjunctivitis in persons 5 years of age and older, when administered prior to and during the grass pollen season?
2. Are the available data adequate to support the safety of Oralair when administered to persons 5 years of age and older? In your deliberations, please consider the available safety data for: children and adolescents (5-17), adults (18-65), and elderly (>65).
 - a. Are the available data adequate to support the safety of Oralair when administered to persons 5 through 9 years of age, with the understanding that auto-injected epinephrine will be made available at home?
 - b. Are the available data adequate to support the safety of Oralair when administered to persons 10 to 65 years of age, with the understanding that auto-injected epinephrine will be made available at home?
3. Please discuss whether the available data support the continued efficacy of Oralair through a) one and b) two years following courses of treatment for the previous three grass pollen seasons.
4. Please comment on what additional studies, if any, should be conducted post-licensure.

The committee was asked to vote on questions 1, 2, 2a and 2b. Questions 3 and 4 were intended for discussion only. The vote for Question 1 was **9** yes, **1** no. The vote for Question 2 was **5** yes,

4 no, 1 abstain. Related to the vote on Question 2, the committee discussed concern about life-threatening local and systemic allergic reactions, particularly those that might occur outside of the physician's office following patient self-administration of ORALAIR. In this regard, the committee recommended access to auto-injectable epinephrine for patients who are prescribed ORALAIR. Also, specific concerns about the safety of ORALAIR in children 5-9 years of age and the lack of data in adults > 65 years of age were noted. The vote for Question 2a was 5 yes, 5 no. The vote for question Q2b was 10 yes, 0 no. In response to Question 3, comments were made about inconsistencies and limitations in the available data proposed to support duration of efficacy beyond three years. In response to Question 4, different subpopulations were suggested for evaluation in postmarketing studies of ORALAIR, including pregnant women, asthmatics and multi-sensitized individuals. In particular, the need for more safety data in children 5-10 years of age was recommended.

9. Other Relevant Regulatory Issues

None.

10. Labeling

Package Insert

CBER's required revisions to the PI included the addition of a Black Box warning to address the risk of severe allergic reactions and the need for access to auto-injectable epinephrine. All issues were acceptably resolved after exchange of information and discussions with the applicant.

Medication Guide

Based on the comments made by the APAC and further internal review, CBER determined that a Medication Guide would be required for inclusion in each packaging unit. All issues were acceptably resolved after exchange of information and discussions with the applicant.

Carton and Container Labeling

All issues, including required revisions to the carton to reference the use of a Medication Guide, were acceptably resolved after exchange of information and discussions with the applicant.

Proposed Proprietary Name

The applicant originally submitted a request for the proposed proprietary name, ORALAIR, to the IND. The APLB reviewer recommended that the name or ORALAIR not be found acceptable because of another CDER drug product that has a similar user population (patients with allergy) and the shared suffix "air" at the end of the proprietary name; because it may increase the risk of medication errors. At the time of review no package insert was available for review. However, OVRP found that the proposed proprietary name, ORALAIR, was "acceptable with concerns." On January 17, 2013, the applicant submitted a request for reconsideration of the proposed proprietary name under the BLA and submitted additional supportive information in order to address FDA concerns. Based on the additional information submitted; the APLB reviewer found the potential for medication errors to be mitigated because of the clear difference and pronunciation in the first syllables of the product name, legibility of a prescribers writing at the beginning of the product name versus the end of the name, the difference between dosage units,

and the way in which pharmacies organize and stock medications. OVRP agreed with this finding.

11.Recommendations and Risk/ Benefit Assessment

a) Recommended Regulatory Action

It is the recommendation of the review committee to approve this product for licensure.

b) Risk/ Benefit Assessment

The data provided in BLA 125471 support the clinical effectiveness of ORALAIR as immunotherapy 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 any of the five grass species contained in this product in persons 10 through 65 years of age. The quality, efficacy and safety data for this product have been thoroughly reviewed and determined to be acceptable for use of this product as indicated in the label. The most common risks associated with ORALAIR are application site reactions such as oral pruritus and throat irritation. No deaths, Intensive Care Unit (ICU) admissions or serious adverse events (SAEs) were reported in any of the studies submitted

The majority of AE associated with ORALAIR are mild or moderate local application reactions. Some patients who experience these mild to moderate local application reactions may discontinue treatment because of discomfort rather than risk.

Clinical studies and post-marketing analysis also indicate that 0.1-0.5% of subjects will experience severe or serious laryngopharyngeal allergic reactions that may compromise upper airway function, or systemic allergic reactions such as anaphylaxis. Most, but not all of these will be associated with the first treatment exposure to ORALAIR. Because of the risk of these severe or serious allergic reactions during home administration, auto-injectable epinephrine will be co-prescribed with ORALAIR. In addition, to inform and educate patients of the potential for severe or serious local or systemic allergic reactions, a Medication Guide will be distributed to all patients who are prescribed ORALAIR.

Finally, because of the concern that the small diameter of the upper airway of younger children may be more easily occluded during a laryngopharyngeal allergic reaction, and because the size of the pre-licensure safety data base for subjects 5-9 years of age was not sufficient to address this concern, the indication of ORALAIR for pediatric subjects is limited to 10-17 years of age. The indication for children 5-9 years of age will be re-evaluated upon completion of safety studies in these children, as mandated by PREA.

c) Recommendation for Postmarketing Risk Management Activities

There was no recommendation for postmarketing risk management activities.

d) Recommendation for Postmarketing Studies

The applicant will conduct a deferred Post Marketing pediatric study under PREA as required by Section 505B (a) of the Food Drug and Cosmetic Act (FDCA) (see section 6 above). In addition, the applicant has agreed to conduct a Phase 4 postmarketing study for continued assessment of ORALAIR safety, subject to 21 CFR 601.70. The study will be an open label, observational study in approximately 6000 patients 10 – 65 years of age with grass pollen-induced allergic rhinitis or conjunctivitis. Subjects will receive ORALAIR approximately 4 months before the expected onset of the grass pollen season and throughout the grass pollen season. Key study dates are as follows:

Key Dates

Final Protocol Submission:	July 31, 2014
Study Start:	First Patient First Visit by February 1, 2015
Study Completion:	December 31, 2017
Clinical Study Report Submission:	June 30, 2018