

Allergenic Products Advisory Committee (APAC) Meeting December 11, 2013

FDA Briefing Document

Biologic License Application (BLA) for *Sweet Vernal, Orchard, Perennial Rye, Timothy, and Kentucky Blue Grass Mixed Pollens Allergen Extract Tablet for Sublingual Use*

Applicant

Stallergenes, Inc

General Information

Product Proper Name: Sweet Vernal, Orchard, Perennial Rye, Timothy, and Kentucky Blue Grass Mixed Pollens Allergen Extract Tablet for Sublingual Use

Proposed Trade Name: ORALAIR®

Description: Sublingual tablet comprised of extracts from five grass pollens mixed together in –b(4)- amounts (by-b(4)-) prior to extraction: Kentucky bluegrass (*Poa pratensis* L.), Orchard (*Dactylis glomerata* L.), Perennial rye (*Lolium perenne* L.), Sweet vernal (*Anthoxanthum odoratum* L.) and Timothy (*Phleum pratense* L.).

Formulation: Each sublingual tablet contains freeze-dried allergen extract of five grasses supplied in a strengths of 100 IR and 300 IR, and contains mannitol, microcrystalline cellulose, croscarmellose sodium, colloidal anhydrous silica, magnesium stearate, and lactose monohydrate as inactive ingredients

Dosing Regimen: The dosing consists of a 3-day dose escalation phase and a maintenance phase. The escalation phase consists of 1 tablet of 100 IR on the first day, 2 tablets of 100 IR on the second day and one 300 IR tablet on the third day. During the maintenance phase, one 300 IR tablet is taken daily.

Applicant: Stallergenes, Inc. (U.S. affiliate of Stallergenes S.A., France)

Proposed Indication and Usage: ORALAIR is indicated for the treatment of grass pollen-induced allergic rhinitis or 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 5 years of age and older.

Abbreviations:

95% CI	95% confidence interval
95% CI UL	upper limit of the 95% CI
AASS	Average Adjusted Symptom Score
AC	allergic conjunctivitis
ACS	Average Combined Score (see CS, below)
AE	adverse event (21 CFR 312.32)
AR	allergic rhinitis
ARC	allergic rhinoconjunctivitis
BAU	Bioequivalent Allergy Units
BLA	Biologics License Application
CS	Combined Score: = $[(RTSS/6) + RMS]/2$
CSR	clinical study report
FAS	full analysis set (essentially equal to the intent to treat subset)
IND	investigational new drug application
IR	index of reactivity (Stallergenes' potency unit for ORALAIR)
RMS	Rescue Medication Score: 0 = no rescue medication taken; 1 = antihistamine, either eye drops or oral, taken; 2 = nasal corticosteroid taken; 3 = oral corticosteroid taken.
RTSS	Rhinoconjunctivitis Total Symptom Score: sum of six RC symptoms (sneezing, rhinorrhea, nasal pruritus, nasal congestion, ocular pruritus and watery eyes), each scored daily by the patient using a 4-point scale from 0 to 3 where 0 = absent and 3 = severe symptoms.
SAE	serious adverse event (21 CFR 312.32)
SCIT	subcutaneous allergen immunotherapy
SLIT	sublingual allergen immunotherapy
SPT	skin prick test
TEAE	treatment emergent adverse event

1.0 Introduction

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 is a more recent development, increasing in popularity in Europe and the US. However, US-licensed allergen extracts for pollens, mold spores, animal danders, insects and inhalants are only approved for use in SCIT.

Stallergenes, Inc. has submitted a Biologics License Application (BLA) to FDA for ORALAIR, a sublingual tablet containing an extract of five grass pollens mixed together in –b(4)- amounts (by –b(4)- prior to extraction: Kentucky bluegrass (*Poa pratensis*), Orchard (*Dactylis glomerata*), Perennial rye (*Lolium perenne*), Sweet vernal (*Anthoxanthum odoratum*) and Timothy (*Phleum pratense*). This tablet is intended to be administered for sublingual immunotherapy (SLIT) in adults, adolescents, and children (5 years of age and older) to treat allergic rhinitis or conjunctivitis due to sensitivity to any combination of these pollens. All five of these grasses belong to the taxonomic (botanical) family *Poaceae* (formerly known as *Gramineae*) and subfamily *Pooideae*. Grass pollen extracts for each of these 5 species have been licensed by FDA to other allergenics manufacturers for SCIT of allergic rhinoconjunctivitis (ARC) to these grass pollens, and these products are standardized according to potency in Bioequivalent Allergy Units (BAU)¹.

The final daily dosage of the tablets proposed for use in the US is 300 IR (index of reactivity)—a Stallergenes “in-house” potency measurement in which 100 IR is defined as the concentration that elicits by skin prick test (SPT) a geometric mean wheal size of 7 mm diameter in 30 subjects who are sensitive to the corresponding allergen². The corresponding range of potency for each lot of tablets will also be provided in BAU, the unitage used by CBER for standardized grass pollen allergen extracts.

As proposed, therapy will begin with an escalation phase in which adults and children will take 100 IR the first day, 200 IR the second day, followed by 300 IR each day. (This dose escalation was used in pediatric trial VO52.06). The medication is to be taken daily beginning four months prior to, and throughout the grass pollen season. The first dose is taken at the healthcare provider’s office, and the remaining doses are taken at home.

2.0 Summary of Clinical Studies

The BLA includes one clinical study conducted in the US under IND, and five studies conducted in Europe (not under IND). Table 1 presents a summary of these clinical studies and the primary efficacy endpoint scores used in each study.

¹ Turkeltaub PC. Use of Skin Testing for Evaluation of Potency, Composition, and Stability of Allergenic Products. *Arb Paul Ehrlich* 1994; 87:79-87

² Nordic Council on Medicines. Registration of allergen preparations, Nordic guidelines. Nordiska Lakemedelsnamnden, Uppsala, Sweden. 1989.

Table 1: ORALAIR® (5-grass pollen extract) sublingual tablet clinical studies and design (Adapted from Table 2-5.1 in the BLA submission)

Study # Location Year conducted	Study Design & Objectives	Study population Age range	Treatment, dose & schedule	Number of Exposed Patients	Treatment Duration	Pre-specified Primary Efficacy Endpoint*
VO34.04 EU 2005	DBPC, randomized, multi-national multicenter Efficacy, Safety	18-45y	500 IR (4M) 300 IR (4M) 100 IR (4M) Placebo Dose escalation	160 155 157 156	-4 months pre-season And ≥ 1 month co-seasonally	ARTSS
VO52.06 EU 2007	DBPC, randomized, multi-national multicenter Efficacy, Safety	5-17y	300 IR (4M) Placebo Dose escalation	139 139	-4 months pre-season and ≥ 1 month co-seasonally	ARTSS
VO53.06 EU, Canada, Russia 2007-2011	DBPC, randomized, multi-national multicenter Sustained efficacy, Post-treatment Efficacy, Safety	18-50y	300 IR (4M) 300 IR (2M) Placebo Direct administration	207 207 219	-4 months pre-season and ≥ 1 month co-seasonally over 3 yrs, followed by 2 subsequent years without study treatment.	AASS
VO56.07A EU 2007-2008	DBPC, randomized, mono-center (allergen exposition chamber study) Efficacy, Safety	18-50y	300 IR Placebo Direct administration	45 44	-4 months	ARTSS
VO60.08 EU 2009	DBPC, randomized, multi-national multicenter Efficacy, Safety	12-65y	300 IR (2M) Placebo Direct administration	188 (n=173 ≥ 18 years of age, n= 15 < 18 years of age) 193 (n= 174 ≥ 18 years of age, n=19 < 18 years of age)	-2 months pre-season and ≥ 1 m co-seasonally	AASS
VO61.08 USA 2009	DBPC, randomized, multi-national multicenter Efficacy, Safety	18-65y	300 IR (4M) Placebo Direct Administration	233 240	-4 months pre-season And ≥ 1 month co-seasonally	CS

*For an explanation of primary endpoint scores see Table 2. EU: Europe; DBPC: Double-blind placebo-controlled; 2M: patients received active treatment starting 2 months prior to the pollen season; 4M: patients received active treatment starting 4 months prior to the pollen season. Dose escalation: subjects in the 300 IR treatment group (Study VO34.04 and VO52.06) and the 500 IR treatment group (Study VO34.04) went through a dose escalation phase in which they took 100 IR on the first day and then, starting on the second day, increasing the dose by 100 IR daily until the final randomized dose was reached.

3.0 Summary of Efficacy

3.1 Clinical Scores for Assessment of Efficacy: There are multiple clinical scoring algorithms that may be used to assess efficacy of immunotherapy. Some of these consider only symptoms or quality of life, some consider medication use, and some take both symptoms and medication use into account. Clinical scores used by the applicant to assess efficacy of ORALAIR in clinical studies submitted in the BLA and the method of calculation are summarized in Table 2.

Table 2: Clinical Scores for Assessment of Efficacy of ORALAIR

Clinical Score	Abbr	Method of Calculation	Min Poss Score	Max Poss Score
Rhinoconjunctivitis Symptom Score	RSS	4-point scale: 0=absent, 1 = mild, 2 = moderate, 3 = severe) for each of six symptoms associated with ARC: sneezing, rhinorrhea, nasal pruritus, nasal congestion, ocular pruritus and watery eyes	0	3
Rhinoconjunctivitis Total Symptom Score ³	RTSS	4-point scale: 0=absent, 1 = mild, 2 = moderate, 3 = severe)	0	18
Average RTSS	ARTSS	RTSS averaged over the duration of a pollen season or the peak of that pollen season for a given subject	0	18
Average Adjusted Symptom Score	AASS	Average of the daily Adjusted Symptom Score (ASS, adjusted for medication use) according to a multi-step algorithm; for details see <i>J Allergy Clin Immunol</i> 128:559; 2011	0	18
Rhinoconjunctivitis Quality of Life Questionnaire ⁴	RQLQ	28 questions in 7 domains (activity limitation, sleep problems, nose symptoms, eye symptoms, non-nose/eye symptoms, practical problems and emotional function), each with a 7-point scale (0 = not impaired at all - 6 = severely impaired). The RQLQ score is the mean of all 28 responses and the individual domain scores are the means of the items in those domains.	0	6
Rescue Medication Score	RMS	0 = no rescue medication taken; 1 = antihistamine, either eye drops or oral, taken; 2 = nasal corticosteroid taken; 3 = oral corticosteroid taken. If a subject took more than one category of rescue medication on the same day, than the rescue medication with the highest score was used.	0	3
Combined (symptom and medication) Score	CS	$CS = [(RTSS/6) + RMS]/2$	0	3
Average Combined Score	ACS	Average of the CS, usually over the whole pollen season or the peak of the pollen season	0	3
Proportion of symptom-controlled days	PSCD	$[(\text{number of symptom and medication free days}) / (\text{number of days in the pollen season})] \times 100$	0%	100%

³ Grouin JM and Vicaut E et al. *Clin Exp Allergy* 2011; 41:1282

⁴ Juniper EF and Guyatt GH. *Clin Exp Allergy* 1991; 21:77

3.2 Clinical Studies Efficacy Analyses

Study VO34.04 (Dose selection study)

This study was conducted in Europe in 2005. A total of 628 adults 18 through 45 years of age with Allergic Rhinoconjunctivitis (ARC) were randomized 1:1:1:1 to receive either placebo or one of three doses of study drug (100 IR, 300IR or 500 IR), for four months prior to the onset of the grass pollen season. Subjects continued treatment through the pollen season. The primary objective was to assess the efficacy of sub-lingual immunotherapy on the ARTSS during the pollen period. Among subjects in the 300 IR and 500 IR groups the ARTSS was similar and statistically lower than the ARTSS in the placebo group.

Study VO52.06 (Pediatric study)

This 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 or study drug for four months prior to the onset of the grass pollen season. Subjects continued treatment through the pollen season. In this study subjects randomized to the study drug received 100 IR on day one, 200 IR on day 2 and 300 IR each day thereafter. The primary objective of this study was to assess the efficacy of ORALAIR 300 IR on the ARTSS. In this study the ARTSS changed in the ORALAIR 300 IR group by -28% (95% CI not provided) compared to placebo.

Study VO53.06 (5 year study)

This 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, 300 IR four months prior to the onset of the grass pollen season or 300 IR two months prior to the onset of the grass pollen season. All subjects were treated prior to and during three consecutive seasons. Subjects recorded AASS during each of the three treatment seasons and two subsequent seasons. The primary objective was to assess the efficacy of ORALAIR on the AASS during the third pollen season and during the 2 years of post-treatment observation. During the third pollen season subjects in the 4 month pre-season treatment group experienced a change of -35% (95% CI UL -19.6%) relative to placebo. However, in Years 4 and 5, during which treatment was discontinued, the 95% CI UL was -5.2% and -6.9% respectively.⁵

Study VO56.07A (Environmental exposure chamber study)

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 or 300 IR for four months. After initiating treatment subjects were exposed to allergen in an EEC on four occasions: week one, month one, month 2 and month 4. The primary objective was to assess the efficacy of ORALAIR on the ARTSS during the last challenge (after 4 months of treatment). After four months of treatment the percent change in ARTSS in the 300 IR group relative to the placebo group was -28.2% (95% CI UL -14.2%).

Study VO60.08 (Two month pre-season treatment study)

⁵ Data recalculated by CBER reviewers from CSRs.

This study was conducted in Europe from February 2009 through August 2009. A total of 381 subjects 12 through 65 years of age with ARC were randomized 1:1 to placebo or 300 IR two months prior to the onset of the grass pollen season. Subjects continued treatment through the pollen season. The primary objective was to assess the safety and efficacy of ORALAIR 300 IR treatment when initiated 2 months prior to the grass pollen season. The primary efficacy endpoint was the Average Adjusted Symptom Score (AASS). In this study the percent change in AASS in the 300 IR group was -8.1% relative to the placebo group; this difference was not statistically significant. Therefore efficacy was not demonstrated.

Study VO61.08 (US efficacy study)

This study was conducted in the US in 2009. A total of 473 adults 18 through 65 with ARC were randomized 1:1 to either placebo or study drug, 300 IR, for four months prior to the onset of the grass pollen season. Subjects continued treatment through the 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 was the CS. This study demonstrated a percent change in LS mean score of -28.2% (95% CI -43.3%, -13.0%) in the ORALAIR 300 IR group compared to placebo.

Summary

Across all 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). For the grass pollen season during which subjects were treated the 95% CI UL for the change in primary endpoint score was between -13.0% and -19.6%.

3.3 Post-hoc Efficacy Analyses Using the Combined Score Algorithm

The studies included in the BLA were conducted over several years and used a number of clinical scoring algorithms as efficacy endpoints.

In the Study VO61.08USA the primary efficacy endpoint was the Combined (Symptom and Medication) Score (CS) – a combination of the symptom score and the rescue medication score. To permit a comparison of efficacy of ORALAIR across field studies the applicant performed post hoc efficacy analyses using the daily CS for subjects treated with ORALAIR 300 IR compared to placebo in studies VO34.04 (Dose selection study), VO52.06 (Pediatric Study), and VO53.06 (Year 1, 2 and 3 of the 5 year study). The results of these analyses and the primary analyses for Study VO61.08USA presented as the percent change in LS Mean are shown in Table 3:

Table 3: Repeated measures ANCOVA of the daily Combined Score (primary analysis set of studies VO61.08USA, VO34.04, and VO52.06 and primary analysis set Year 1, 2 and 3 of study VO53.06)

Treatment	n	LS Mean	Percent change LS Mean relative to placebo	
			Point estimate	95% CI
Study VO61.08USA^b				
300 IR (4M)	208	0.32	-28.2%	-43.4%, -13.0%
Placebo	228	0.45		
Study VO34.04^{b,d}				
300IR (4M)	136	0.50	-29.6%	-43.1%, -16.1%
Placebo	148	0.70		
Study 52.06^d				
300 IR (4M)	131	0.44	-30.1%	-46.9%, -13.2%
Placebo	135	0.63		
Study VO53.06 Year 1 Treatment^{c, d}				
300 IR (4M)	188	0.56	-16.4%	-27.0%, -5.8%
300 IR (2M)	188	0.53	-20.7%	-31.3%, -10.1%
Placebo	205	0.67		
Study VO53.06 Year 2 Treatment^{c, d}				
300 IR (4M)	160	0.35	-38.0%	-53.4%, -22.6%
300 IR (2M)	155	0.35	-38.3%	-54.0%, -22.7%
Placebo	172	0.56		
Study VO53.06 Year 3 Treatment^{c, d}				
300 IR (4M)	149	0.31	-38.3%	-54.7%, -22.0%
300 IR 2M	147	0.29	-40.9%	-57.4%, -24.5%
Placebo	165	0.50		

* Studies VO34.04 and VO52.06, intent-to-treat population; all other studies, FAS

CI = Confidence Interval; IR = Index of Reactivity; LS = Least Squares;

n: Number of evaluable patients for the statistical model

300 IR (4M) = patients received active treatment starting 4 months prior to the pollen season

300 IR (2M) = patients received active treatment starting 2 months prior to the pollen season

^b Statistical method = model using Restricted Maximum Likelihood (REML)

^c Statistical method = model using Minimum Variance Quadratic Unbiased Estimation (MIVQUE0)

^d *Post hoc* analysis Modified from Section 2.7.3 Summary of Clinical Efficacy Table 2.7.3-38 and Table 2.7.3-55

In these post-hoc analyses subjects treated with 300 IR for 4 months prior to the pollen season had a reduction in CS relative to placebo subjects. Across all studies the 95% CI UL for the percent change in CS ranged from -5.8% (Study VO53.06 Year 1) to -24.5% (Study VO53.06 Year 3). These results are consistent with the results of the primary analyses presented above in Section 3.2.

4.0 Summary of Safety

4.1 Overall Clinical Studies Safety Database

Across clinical studies submitted to the BLA, a total of 2,512 participants were randomized to receive ORALAIR (1,514 participants) or placebo (998 participants). Safety analyses presented herein are based on two pooled analyses:

- all adults ≥ 18 years of age at entry who received ORALAIR at a daily dose of 300 IR or placebo (includes adults enrolled in seven studies⁶)
- all children and adolescents 5 to 17 years of age at entry who received ORALAIR at a daily dose of 300 IR or placebo (includes children and adolescents enrolled in two studies)

Overall, 1,192 persons received ORALAIR at a daily dose of 300 IR, including 1,038 adults ages 18 through 64 years, 67 adolescents ages 12 through 17 years, and 87 children ages 5 through 11 years. Placebo recipients included 840 adults ages 18 through 64 years, 84 adolescents ages 12 through 17 years, and 74 children ages 5 through 11 years. Among adult study participants, the mean age was 31.5 years in the ORALAIR 300 IR groups and 32.1 years in the placebo groups. Among child and adolescent study participants, the mean age was 10.9 years in the ORALAIR 300 IR groups and 11.6 years in the placebo groups. All randomized participants who received at least one dose of ORALAIR or placebo were included in the analyses of safety presented herein.

The mean duration of exposure to ORALAIR 300 IR was 224.2 days (range 0-597 days) for adults and 149.9 days (range 12-197 days) for children and adolescents. For adult exposure, the lower end of the range, 0, reflects withdrawal from one study of five participants who were randomized to a group that received placebo for two months prior to an ORALAIR regimen, but who withdrew prior to receiving any ORALAIR. The mean duration of exposure in the respective placebo recipients was similar to that observed in the ORALAIR recipients. The difference in duration of exposure in adults and children/adolescents reflects differences in study designs.

Across all clinical trials, 17% of randomized participants had intermittent asthma at baseline. Among the adult study participants, 179 participants who received ORALAIR at a daily dose of 300 IR and 149 participants who received placebo had a history of intermittent asthma. Among children and adolescents, 32 participants who received ORALAIR at a daily dose of 300 IR and 34 participants who received placebo had a history of intermittent asthma.

Safety was monitored through the use of diary cards and inquiry about adverse events at study visits.

⁶ Analysis includes 11 subjects from study VO33.04DK, a small dose-ranging study performed in Denmark and not otherwise included in this Briefing Document.

4.1.2 Clinical Studies Pooled Safety Analyses- Adults

Withdrawals due to Treatment Emergent Adverse Events

In the adult pooled analysis, 4.7% (49/1038) of ORALAIR recipients and 1.1% (9/840) of placebo recipients withdrew from study participation due to a treatment emergent adverse event (TEAE, any adverse event that occurred from the administration of the first dose of study product up to the 30th day after the last administration of the study product). TEAEs leading to study withdrawal in 2 or more (range 2-5) adults who received ORALAIR were oral pruritus, upper abdominal pain, vomiting, pharyngeal edema, dyspepsia, dysphagia, mouth edema, esophageal pain, tongue edema, throat irritation, conjunctivitis, and chest discomfort.

Treatment Emergent Adverse Events

Several TEAEs were reported at a higher frequency following ORALAIR than placebo. Of TEAEs reported at a higher frequency following ORALAIR 300 IR, the most commonly reported were oral pruritus (32.6% ORALAIR; 6.6% placebo) and throat irritation (21.1% ORALAIR; 3.8% placebo)⁵. Other TEAEs reported in >2.5% of ORALAIR recipients and at a higher frequency than placebo recipients included mouth edema, tongue pruritus, lip edema, oral parasthesia, dyspepsia, tongue edema, sneezing, cough, rhinorrhea, nasal discomfort, oropharyngeal pain, allergic rhinitis, pharyngeal edema, rhinitis, eye pruritus, increased lacrimation, conjunctivitis and ear pruritus.

Serious Adverse Events

In the 300 IR study groups, at least one serious TEAE was reported in 13 (1.3%) ORALAIR recipients and 5 (0.6%) placebo recipients.

In addition to the two laryngopharyngeal disorders described below, which were considered by the Investigator to be certainly related to ORALAIR, one serious adverse event was considered by the Investigator to be possibly related to ORALAIR. A 43-year-old female presented with gastroenteritis 93 days after initiating ORALAIR. She was hospitalized and treated with antibiotics. She recovered from the gastroenteritis within approximately one week. She discontinued ORALAIR and withdrew from the study.

Anaphylaxis

No cases of anaphylaxis or use of epinephrine were reported.

Severe Laryngopharyngeal Disorders

Two ORALAIR recipients reported laryngopharyngeal disorders.

A 30-year-old male experienced severe laryngeal edema and redness of the face within 5 minutes after receiving the first dose of ORALAIR. He received intravenous prednisolone. The event resolved within 30 minutes. He discontinued ORALAIR and withdrew from the study. The Investigator considered the event certainly related to ORALAIR.

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. Recovery by day 3 was reported. She discontinued ORALAIR and withdrew from the study. The Investigator considered the event certainly related to ORALAIR.

Deaths

There were no deaths reported in study participants.

4.1.3 Clinical Studies Pooled Safety Analyses - Children and Adolescents

Withdrawals due to Treatment Emergent Adverse Events

In the children/adolescents pooled analysis, 5.2% (8/154) of ORALAIR recipients and 1.3% (2/158) of placebo recipients withdrew from study participation due to a TEAE. TEAEs leading to study withdrawal in children or adolescents who received ORALAIR were oral pruritus, mouth edema, vomiting, chest discomfort, and oropharyngeal blistering.

Treatment Emergent Adverse Events

In the European pediatric study VO52.06, several TEAEs were reported at a higher frequency following ORALAIR than placebo. Of TEAEs reported at a higher frequency following ORALAIR, the most commonly reported were 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 and at a higher frequency than placebo recipients included nasal congestion, asthma, dysphonia, oropharyngeal pain, tongue pruritus, lip edema, tongue edema, lip pruritus, upper abdominal pain, vomiting, tonsillitis, bronchitis, upper respiratory tract infection, eye pruritus, atopic dermatitis, pyrexia, and ear pruritus. For some of these events, the magnitude of the difference in frequency between the groups was marginal (e.g., upper abdominal pain 2.6% ORALAIR and 2.5% placebo; pyrexia 3.9% ORALAIR and 3.2% placebo; nasopharyngitis 13.7% ORALAIR and 12.9% placebo).

Serious Adverse Events

At least one serious TEAE was reported in 1 (0.6%) ORALAIR recipient and 2 (1.3%) placebo recipients. None of these serious TEAEs were considered by the investigator to be related to the study product. The serious TEAE in the ORALAIR group was a mild exacerbation of asthma.

Anaphylaxis

No cases of anaphylaxis or use of epinephrine were reported.

Severe Laryngopharyngeal Disorders

No cases of severe laryngopharyngeal disorders were reported.

Deaths

There were no deaths reported in study participants.

4.2 Post-Marketing Safety Data

ORALAIR was first granted marketing authorization in 2008 in Germany and is currently marketed in 16 countries. The applicant provided safety data from two observational post-authorization studies conducted in Germany as well as safety data from spontaneous reports.

Post-Marketing Surveillance Studies

At the request of the German Health Authority, the applicant conducted two observational post-authorization studies to monitor the safety of ORALAIR.

In one study, conducted in 2008, a total of 808 adults and 91 children and adolescents were treated with ORALAIR. The overall mean duration of treatment per patient was 191.2 days. In this study, 85 patients (9.5%) withdrew due to adverse events. The most frequent event that led to premature study discontinuation was mouth edema. Based on a summary submitted to the BLA, serious adverse events were reported in 6 patients (all adults), as listed below:

- severe laryngopharyngeal disorder on treatment Day 3
- severe oral pruritus, mild oral mucosa swelling, swallowing difficulty and dysphagia on Day 1 followed by severe aggravation of Crohn's disease on Day 16
- severe plasmacytoma (unknown day)
- moderate burning eyes on Day 199
- malignant melanoma (unknown day)
- severe lip and tongue swelling on Day 7

In the second study, conducted in 2009, a total of 829 patients (457 children between 5 and 11 years old and 372 adolescents between 12 and 17 years old) were treated with ORALAIR. The overall mean duration of treatment per patient was 190.2 days. In this study, 76 patients (9.2%) withdrew due to adverse events. The most frequent event that led to premature study discontinuation was throat irritation. Based on a summary submitted to the BLA, serious adverse events were reported in 6 patients, as listed below:

- A 10 year old boy with a previous history of asthma experienced an anaphylactic reaction described as edema of both lips associated with itching in palms of hands and in ear canal, 3 minutes after ORALAIR intake. There was no respiratory or circulatory system involvement. He fully recovered after treatment with prednisone administered rectally. Treatment with ORALAIR was discontinued. The applicant assessed the reaction as angioedema of the lips.

- throat irritation associated with dyspnea and flushing
- tongue edema, pharyngeal edema and dyspnea
- aggravated atopic dermatitis associated with eye pruritus, eyelid injury and conjunctivitis
- aggravated atopic dermatitis associated with pruritic rash
- Samter's triad

All of these serious adverse events but one (Samter's triad) were considered related to ORALAIR administration.

Search of Post-Marketing Safety Database for Adverse Reactions of Special Interest

The applicant provided analyses of adverse events received from spontaneous reports during the period June 2008 through June 2012. The applicant provided estimates of exposure to ORALAIR in patient years for adults and children based on sales figures, treatment regimen, and data from Germany on distribution by age. However, the accuracy of these estimates, subject to several assumptions, is unclear. Thus, for data from passive post-marketing surveillance, rates will not be provided.

Anaphylactic Reactions

From a broad standardized MedDRA query search for anaphylactic reaction, 24 serious reports were retrieved. Upon review, 4 cases were assessed by the applicant as possible anaphylactic reactions. Two of these 4 cases occurred in adults and two occurred in children (age 9 years and 12 years, respectively). In addition, one case of hypotension in an adult that was not retrieved by the query was considered by the applicant as a possible anaphylactic reaction. Of the five cases, three occurred within 15 minutes after the first intake of ORALAIR, one occurred on Day 7 of treatment, and one occurred approximately 7 weeks after initiation of treatment. Two of the patients had a history of controlled asthma and one had a history of myocardial infarction, hypertension and diabetes. The case that occurred approximately 7 weeks after initiation of treatment was thought to be consistent with "food-dependent exercise-induced anaphylaxis" and unlikely related to ORALAIR.

Severe Laryngopharyngeal Reactions

From a standardized MedRA query search, using a broad list of preferred terms suggestive of severe laryngopharyngeal reactions, 46 cases were retrieved. Cases which resolved spontaneously or after administration of oral antihistamines and/or inhaled beta2 agonists or inhaled corticosteroids (23 cases) and cases with no respiratory symptoms (10 cases) were excluded from analysis since they were not consistent with severe reactions. In addition, two cases were excluded after medical review because it either did not correspond to a severe laryngopharyngeal disorder or was not considered related to ORALAIR by both the reporter and the applicant. The remaining 11 cases (8 reported in adults and 3 in children or adolescents) were considered severe laryngopharyngeal disorders. They generally occurred within the first two weeks of treatment (82% of cases) with about 45% occurring after the first intake.

5.0 Allergenic Products Advisory Committee

The BLA includes data evaluating the safety and efficacy of ORALAIR, 300 IR per dose, for immunotherapy of allergic rhinitis or conjunctivitis due to sensitivity to any combination of the five grass pollens included in the product. The proposed treatment regimen includes a 2-day ramp up of dosing (100 IR day 1, 200 IR day 2), followed by daily dosing with 300 IR for 4 months prior to the onset of grass pollen season, to be continued through the duration of the season.

On December 11, 2013, the Allergenic Products Advisory Committee will be asked whether the available data support the safety and the efficacy of the product in persons 5 years of age and older. In addressing this question, the Committee should address safety and efficacy for adult and pediatric patients separately.

The Committee will be asked to discuss recommendations regarding the need, if any, for additional studies.