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Priority Review	
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Supervisory Concurrence	<b>APPROVED</b> By Jay E. Slater, MD at 9:59 am, Mar 20, 2014
Applicant	Stallergenes, Inc.
Established Name	ORALAIR® (Sweet Vernal, Orchard, Perennial Rye, Timothy, and Kentucky Blue Grass Mixed Pollens Allergen Extract) Tablet for Sublingual Use
(Proposed) Trade Name	Oralair
Pharmacologic Class	Allergenic extract
Formulation(s), including Adjuvants, etc	Tablet of comprised of extracts from five grass pollens mixed together in equal amounts (by mass) prior to extraction: Kentucky bluegrass ( <i>Poa pratensis</i> L.), Orchard ( <i>Dactylis glomerata</i> L.), Perennial rye ( <i>Lolium perenne</i> L.), Sweet vernal ( <i>Anthoxanthum odoratum</i> L.) and Timothy ( <i>Phleum pratense</i> L.). All five of these grasses belong to the taxonomic (botanical) family <i>Poaceae</i> (formerly known as Gramineae) and subfamily <i>Pooideae</i> .
Dosage Form(s) and Route(s) of Administration	Sublingual (placed beneath the tongue until dissolved)
Dosing Regimen	300 IR (index of reactivity) per tablet, once per day
Indication(s) and Intended Population(s)	ORALAIR is an allergen extract sublingual tablet indicated as immunotherapy 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 contained in this product [11]. ORALAIR is approved for use in persons 10 to 65 years of age.

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## 1. EXECUTIVE SUMMARY

### Background

ORALAIR® is a tablet comprised of extracts from five grass pollens mixed together in equal amounts (by mass) prior to extraction: Kentucky bluegrass (*Poa pratensis*), Orchard (*Dactylis glomerata*), Perennial rye (*Lolium perenne*), Sweet vernal (*Anthoxanthum odoratum*) and Timothy (*Phleum pratense*). All five of these grasses belong to the taxonomic family *Poaceae* (formerly known as Gramineae) and subfamily *Pooideae*. Extracts from each of these five grass pollens are manufactured domestically and approved by the FDA for subcutaneous immunotherapy (SCIT) of allergic rhinoconjunctivitis (ARC), and are standardized according to potency in Bioequivalent Allergy Units (BAU). This tablet is manufactured in Europe by mixing the five pollens together prior to making the extract, which is then refined into tablet form for sublingual administration (sublingual immunotherapy, SLIT) for ARC due to allergic sensitivity to any combination of these pollens.

ORALAIR® is currently marketed throughout the European Union, and has completed Phase 3 testing in the US. As in Europe, the dosage of the tablets to be used in the US is 300 IR (index of reactivity)—an 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 allergen. In addition to defining potency in IR, the package insert will also state the corresponding range of potency of each lot of tablets in BAU, the unitage used by CBER for grass pollens.

The sponsor states that clinical experience has demonstrated that many of the subjects who do not tolerate the product will experience the AE at the time of the very first dose. Therefore, first dose is taken at the physician's office, and the remaining doses are taken at home. To minimize the severity of those AE, adults and children will “ramp up” dosage over three days—100 IR the first day, 200 IR the second day, and 300 IR each successive day. The medication is to be taken daily beginning four months prior to, and throughout the grass pollen season (GPS, which runs from May through September in the mid-Atlantic region of the US). Clinical Protocol V056.06 demonstrated that efficacy may be sustained for as long as two years after taking the medication for three consecutive years (each year 4 months prior to GPS and then throughout GPS). It is expected that the product will be taken for multiple years, particularly by those who tolerate it with minimal side effects.

### Overview of Submitted Studies

The BLA includes review of five studies conducted in Europe (none of these were under IND), and a pivotal clinical trial that was conducted in the US that was proposed in the original IND 13776 submission. The European trials include one Phase 2 trial (VO34.04), a dosing study that demonstrated that the 300 IR was comparably efficacious to the 500 IR dose but with fewer AE.

Of the European Phase 3 trials (VO52.06, VO53.06, and VO60.08), VO52.06 studied safety and efficacy in children ages 5-17y, and clinical trial VO53.06 studied adults, 18-50y of age. Both these trials demonstrated that the product was safe and effective for the treatment of ARC in their respective study populations. Study VO53.06 was a five-year study in which subjects were treated for three years, and observed for sustained efficacy for the following two years. The data demonstrate that efficacy is maintained for at least one year and possible two years, but does appear to wane.

Clinical trial VO60.08 studied adolescents and adults—ages 12-65y. Rather than treating for four months prior to grass pollen season (GPS), subjects in this study were treated for only two months. Clinical trial VO60.08 affirmed the safety of the product, but did not demonstrate efficacy.

The pivotal Phase 3 US trial was initiated and completed in 2009 (IND 13776), and studied a total of 473 adults with ACS who were treated with either placebo or study drug, 300 IR, for four months prior to the onset of GPS and then continued throughout the GPS season. The primary endpoint was the Average Combined Score (ACS, symptom scoring of these studies is explained below), and demonstrated an improvement in the ACS among subjects in the ORALAIR study drug group compared to placebo, and an acceptable safety profile of the study drug.

#### Review of Efficacy

The totality of the clinical studies supports the sponsor's assertion that the product is effective for the treatment of ARC due to any of the grass pollens included in ORALAIR. The improvement in the combined symptom and medication scores is ~15-30% over placebo, which the Agency considers clinically meaningful.

#### Review of Safety

Across clinical trials submitted to the BLA, 1,192 subjects received ORALAIR 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. The 998 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. ORALAIR has not been studied in adults over 65 years of age.

The study subject criteria for all clinical studies excluded subjects with asthma that required therapy other than intermittent  $\beta$ -agonists, and excluded subjects with concomitant diseases that are common in the US, such as adults with chronic diseases, including heart disease and diabetes mellitus. Upon licensure, however, the general subject population will include many subjects who would have been excluded from these studies, including children and adults with asthma greater than "mild" severity, and maximum age of 50 years. In this population, the rate and severity of AE may be greater than observed in the clinical trials. Therefore, the safety profile of the product in the



clinical trial population may not accurately reflect the rate and severity of AE in the general population of patients who will use ORALAIR.

In addition, safety has been monitored since the product was licensed in Germany in 2008 on a “named-subject” basis, an intermediate between investigational status and full licensure. The sponsor reports 65,483 subject-years including 20,939 subject years for children and adolescents 5-17 years of age. This population includes 808 adults and 920 children in two German observational Post-authorization safety studies (PASS).

Among the adults who participated in the clinical trials, 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). All TEAEs reported in >2.5% of ORALAIR recipients were local application reactions in the mouth and oropharynx, or those associated with ARC. Two of these TEAE were SAE that were definitely related to the study drug. Both were severe laryngopharyngeal disorders that occurred immediately after the first dose. There were no cases of self-administration of epinephrine, and there were no deaths.

In the clinical trials, 4.7% (49/1038) of adult ORALAIR recipients and 1.1% (9/840) of adult placebo recipients withdrew from study participation due to a TEAE. TEAE leading to study withdrawal in two or more (range 2-5) adults who received ORALAIR were local application reactions and ARC symptoms, as well as upper abdominal pain, vomiting, pharyngeal edema, dyspepsia, dysphagia, and chest discomfort. Many but not all TEAE that were related to treatment occurred after the first administration of study drug.

In general, the pediatric safety data are consistent with the adult safety data. 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, and these were largely restricted to local application reactions and symptoms of ARC. Unlike the adults, vomiting and atopic dermatitis were also reported as TEAE in > 2.5% of ORALAIR recipients. There were no reports of epinephrine use, anaphylaxis, severe laryngopharyngeal disorders or deaths in children or adolescents.

In the total European post-marketing database, there were four SAE, three of which may possibly be anaphylaxis. These three SAE occurred within minutes of taking the first dose of ORALAIR in the physician’s office. The fourth case occurred at home in a 9 year old male with “well controlled intermittent asthma” who had mild tingling and slight throat swelling after the first six doses of ORALAIR (which should have warranted discontinuation of the drug). On Day 7 of therapy, he was short of breath due to upper airway swelling and required epinephrine IM. Most interesting, two of the four subjects, would probably have been excluded from the controlled trials—the 9 year old boy had asthma that required control (presumably inhaled corticosteroids), and a 58 year old

female with a history of myocardial infarction, hypertension, and diabetes mellitus. These post-marketing reports validate safety concerns regarding a patient population that is more complex than the subjects included in the clinical studies conducted for approval of the product.

Finally, this tablet requires as long as 60 seconds to dissolve, which may be longer than young children are willing to keep the tablet beneath the tongue. Members of the Allergic Products Advisory Committee (APAC) expressed concern about the safety of ORALAIR in children less than 9 years of age because of the enhanced risk of EoE in children who may not be able to hold the tablet under the tongue. The Paul-Ehrlich Institute (PEI) has requested close monitoring for eosinophilic syndromes in the post-market setting after reviewing the 7<sup>th</sup> PSUR for ORALAIR but, in a separate communication with PEI, no safety signal has been noted.

#### Pediatric Research and Equity Act

This product was reviewed by the PeRC March 19, 2014. The sponsor asked that PREA be waived for children less than 5 years of age because seasonal allergies are uncommon in this population. As stated on the PREA Waiver Plan Assessment for this product, “Studies are impossible or highly impractical” for children less than 5 years of age.

#### Pharmacovigilance

A full Pharmacovigilance Plan Review was submitted on or about June 24, 2013. The sponsor proposes to continue routine Pharmacovigilance in accordance with ICH Guidance E2E. Expedited AE and periodic safety reports will be submitted to FDA. These events are subject to enhanced surveillance: allergic reactions including severe laryngopharyngeal disorders, autoimmune disease, and anaphylaxis. CBER agrees with the proposed plan, but has one post-marketing requirement:

- An open label study in ~300 children 5 - 9 years of age who are allergic to grass pollens contained in ORALAIR. Subjects will receive ORALAIR for 30 days and will be followed for the occurrence of local and systemic adverse events (AEs) that result in medical attention (e.g., epinephrine use, hospitalization, and/or an ER visit). In addition, potential risk factors for any AEs that occur should be assessed as secondary objectives based on information obtained in evaluation of events. Such risk factors would include, but not be limited to month of year when event occurs, age, antecedent interruption of therapy, and use of any concomitant medication including allergen immunotherapy. AEs will be monitored by a diary card that will survey for specific events.

In addition, the sponsor has committed to the following:

- A Phase 4 safety study of 6,000 patients 10-65 for 30 days to survey for AE. The study population will be patients who are prescribed ORALAIR in the European Union and the US. Patients will be followed for the occurrence of local and systemic adverse events (AEs) that result in medical attention (e.g., epinephrine use, hospitalization, and/or an ER visit). In addition, potential risk factors for any AEs that occur should be assessed as secondary objectives based on information

obtained in evaluation of events. Such risk factors would include, but not be limited to month of year when event occurs, age, antecedent interruption of therapy, and use of any concomitant medication including allergen immunotherapy. AEs will be monitored by a diary card that will survey for specific events.

#### Clinical Reviewer Summary

ORALAIR is effective for the treatment of ARC that is the consequence of allergy to any of the five grass pollens included in the extract. Since subjects who are allergic to Johnson, Bahia, or Bermuda grass pollens were excluded from each of the studies, and since these grasses pollinate during the same time period as those included in the 5-grass mixture, subjects who are allergic to these grasses may not experience reduction of grass allergy symptoms to the same degree as those in the study populations.

The first administration of ORALAIR must be in the office of a health care provider who is experienced in the treatment of allergic reactions that may cause constriction of the upper airway, wheezing, or anaphylaxis.

For those subjects who tolerate the first dose, ORALAIR is generally safe for at home use. However, there are the following safety issues:

1. ORALAIR has not been studied in adults over 65 years of age
2. Differences in morbidity between the study population and general population who will use the approved drug.
3. Potential for life-threatening local and systemic reactions
4. Small clinical database in children 5-9 years of age

To address these safety issues, the proposed indication will be amended. The proposed indication is:

“ORALAIR® (5-grass pollen extract) sublingual tablet is indicated for the treatment of grass pollen-induced allergic rhinitis or conjunctivitis in adults, adolescents, and children (5 years of age and older) with a clinical history confirmed by positive skin test or in vitro testing for grass pollen-specific IgE antibodies.”

The amended indication is:

“ORALAIR® (5-grass pollen extract) sublingual tablet is indicated for the treatment of allergic rhinitis or conjunctivitis in children, adolescents, and adults 10-65 years of age with a clinical history confirmed by positive skin test or in vitro IgE testing for sensitivity to any of the five grass pollens included in the product.”

The proposed dose of ORALAIR for children is 100 IR the first day, 200 IR the second day, and 300 IR thereafter. The reviewer agrees with this proposed dosing.

The sponsor originally proposed that consistent with the clinical studies, that the first dose of ORALAIR is 300 IR in adults. Subsequently, the sponsor proposed that the dosing for adults include the “ramp up” from 100 IR to 300 IR that was proposed for children. The clinical reviewer recommends that the Agency reject the proposed amendment because 1) the ramp-up may have the unintended consequence of a patient

experiencing a life-threatening reaction to ORALAIR upon reaching the full dose at home, rather than taking the full dose on Day 1 in the health care setting; and 2) ORALAIR was administered to adults in a dose of 300 IR without ramp-up, and there are no data that demonstrate that the ramp-up in adults is equally safe or safer than dosing without ramp-up.

In addition to limiting the age to patients between 10 and 65 years of age, the package insert will include a boxed warning that addresses the potential of life-threatening local and systemic reactions which warrant the consideration of a prescription for an epinephrine self-administration device (ESAD). A medication guide must be distributed to patients to insure that they are informed of these risks; the importance of having an ESAD at home, and that in the instance of recurring local application site reactions, patients should discontinue ORALAIR until further directed by the prescribing health care provider.

## **2. CLINICAL AND REGULATORY BACKGROUND**

### **2.1 Background**

Allergic rhinoconjunctivitis (ARC) is a worldwide disease affecting over 500 million people, including approximately 30 million Americans. Grass pollen is a major seasonal allergen in the US. Untreated or inadequately treated ARC causes sleep disturbance, daytime fatigue and somnolence as well as depressed mood, irritability, and behavioral problems. Societal costs include absenteeism from work or school and decreased productivity at work.

In addition to allergen avoidance, current treatment options include pharmacologic therapy such as oral antihistamines and nasal corticosteroids, which provide temporary relief from allergy symptoms, but are not effective in all subjects.

Another treatment option for ARC is immunotherapy. Immunotherapy involves the administration of gradually increasing doses of the allergen over a period of time to desensitize the subject. It is the only known treatment that modifies the immune response and treats the cause rather than the symptoms. In the US, the only licensed route of administration is subcutaneous injection (SCIT). Despite the documented benefits of SCIT, only 5% of the US population with allergic rhinitis, asthma, or both receive SCIT because of its discomfort, the risk of local and systemic allergic reactions, and the inconvenience of frequent injections which should be administered only in the health care setting.

An alternative to SCIT is sublingual immunotherapy (SLIT). As its name implies, the medication is kept beneath the tongue where it is absorbed into the mucosa. Through complex and not fully characterized mechanisms, administration of allergens through the oral, gingival, or sublingual mucosa can decrease the allergic response thus desensitizing the subject by modifying disease at least temporarily if not permanently (i.e. inducing tolerance). In addition, and perhaps most importantly, published studies suggest that the incidence of severe or serious AE associated with SLIT is significantly lower than with SCIT such that SLIT may be safe for self-administration at home. A recent Cochrane review based on review of SLIT studies suggested that SLIT is a viable alternative to SCIT with a significantly lower risk profile and little difference in overall efficacy (Radulovic S., Calderon M. A., Wilson D.,

Durham S. Sublingual immunotherapy for allergic rhinitis. *Cochrane Database Syst Rev.* 2010;12:CD002893).

Stallergenes SA is a French biopharmaceutical corporation that focuses on the treatment of allergic disease. In Europe, Stallergenes markets one solution for SLIT as a “named subject product,” and the sublingual immunotherapy tablet, ORALAIR®, that is the subject of this BLA. ORALAIR® is a tablet of comprised of extracts from five grass pollens mixed together in equal amounts (by mass) prior to extraction: Kentucky bluegrass (*Poa pratensis*), Orchard (*Dactylis glomerata*), Perennial rye (*Lolium perenne*), Sweet vernal (*Anthoxanthum odoratum*) and Timothy (*Phleum pratense*). All five of these grasses belong to the taxonomic family *Poaceae* (formerly known as Gramineae) and subfamily *Pooideae* and are among the standardized grasses approved by the FDA for the skin-test diagnosis and SCIT.

ORALAIR® was approved in the European Union in 2012, and has successfully completed Phase 3 testing in the US. The sponsor proposes the following indication:

“ORALAIR® (5-grass pollen extract) sublingual tablet is indicated for the treatment of grass pollen-induced allergic rhinitis or conjunctivitis in adults, adolescents and children (5 years of age and older) with a clinical history confirmed by positive skin test or *in vitro* testing for grass pollen-specific IgE antibodies. In adults, pre- and co-seasonal treatment with ORALAIR® (5-grass pollen extract) sublingual tablet for 3 years provides efficacy for at least two years after treatment cessation.”

As in Europe, the dosage of the tablets to be used in the US is 300 IR (index of reactivity)—an 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 allergen. In addition to defining potency in IR, the package insert will also state the corresponding range of potency of each lot of tablets in bioequivalent allergy units (BAU), the potency units used by CBER for grass pollens.

Adults will initiate therapy at 300 IR per day (one tablet, sublingually administered per day). Upon approval for use by children, they will “ramp up” dosage over three days—100 IR the first day, 200 IR the second day, followed by 300 IR each day. The medication is to be taken daily beginning four months prior to, and throughout the grass pollen season (GPS, which runs from May through September in the mid-Atlantic region of the US).

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

Allergic rhinitis (AR) is characterized by red, itchy eyes, a blocked and runny nose, and sneezing. The most common causes of allergic rhinitis are different pollens (grass and tree), house dust mites, mold and animal dander. Allergic rhinitis can be intermittent (such as hay fever) or persistent (all year round). Often AR is accompanied by allergic conjunctivitis (AC), and may be accompanied by allergic asthma. About 10% of adults and children in the US have AR, AC, or both (ARC).

ARC is an inflammatory disease that is mediated by IgE specific to the seasonal or perennial allergen. IgE binds to mast cells that reside in the nasal mucosa, which upon cross-linking the IgE by allergen, are triggered to release mediators such as histamine, leukotrienes, and prostaglandins that are responsible for the immediate reaction. The

activated mast cells also release inflammatory proteins that induce migration of eosinophils, neutrophils and lymphocytes, eliciting a so-called late phase reaction.

According to the ARIA guideline (Allergic Rhinitis and its Impact on Asthma, *J Allergy Clin Immunol* 130:1049; 2012), symptoms occurring fewer than four days a week or fewer than four weeks at a time are considered Intermittent AR, and greater than either of those is considered persistent AR. In addition to frequency, AR is classified according to severity, the index of which is quality of life, which then determines approach towards treatment. Mild AR does not interfere with sleep, and such daily activities as work or school. Mild AR is generally treated with pharmacologics such as oral decongestants with or without antihistamines (either topical or oral) or a nasal leukotriene receptor antagonist. For moderate AR, intranasal corticosteroids or agents that block mast cell degranulation may be added to the pharmacologic regimen. Severe symptoms are those that impair sleep, and daily activities such as sport, leisure, work or school. Severe AR is often treated with allergen immunotherapy.

Because either there are multiple mechanisms by which immunotherapy modifies disease or the precise mechanism has not been defined, there are no serologic or tissue biomarkers that correlate with the severity of AR, or the response to immunotherapy. Therefore, the severity of AR, and response to therapy, is quantified by quality of life scores, the most common of which is assigning a score each to a set of clinical symptoms and to pharmacologic medications that are used to alleviate those symptoms, and averaging the two scores—often referred to as the average combined score (ACS). Currently, a decrease in ACS by 15-20% from baseline is considered a clinically meaningful improvement that enhances the quality of life, also known as the Minimal Clinically Important Difference.

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

### *Pharmacologic agents used to treat AR*

The table below summarizes the efficacy of pharmacologic agents used to treat ARC. A short discussion of each agent follows the table. The primary sources for the discussion Greiner N and Hellings PW et al. *The Lancet* 178:2112; 2012, and , Sanjay NM, Shah JH, and Thennati, R. *Internat Immunopharm* 11:1646; 2011.

**Table 1. Pharmacologic agents to treat ARC**

Drug class	Route of administration	Most effective	Moderately effective	Least effective
Antihistamines	p.o.	Sn, Rh, It	Op	Co
Antihistamines	i.n.	Rh	Sn, Co, It	Op
Corticosteroids	i.n./p.o.	Sn, Rh	Co, It	Op
Mast cell stabilizers	i.n.	–	–	Sn, Rh, It, Co, Op
Decongestants	i.n.	–	Co	Sn, Rh, It, Op
Decongestants	p.o.	–	–	Co, Sn, Rh, It, Op
Anticholinergics	i.n.	Rh	–	Sn, It, Op, Co
Antileukotrienes	p.o.	–	Co, Op	Sn, Rh, It

Differential response to allergic rhinitis symptoms by different drug classes as per ARIA (Allergic Rhinitis and its Impact on Asthma) guidelines.

Sn—sneezing, Rh—rhinorrhea, It—nasal itching, Op—ophthalmic symptoms, Co—nasal congestion.

Adapted from: Sanjay NM, Shah JH, and Thennati, R. *Internat Immunopharm* 11:1646; 2011

### Decongestants

Decongestants are often the first line of treatment for AR. Oral (e.g. pseudoephedrine) and topical decongestants (oxymetazoline) can be purchased without a prescription, are relatively inexpensive, and are non-sedating. Pseudoephedrine and other decongestants are vasoconstrictors that reduce tissue hyperemia, edema, and nasal congestion. The decongestants also increase the drainage of sinus secretions, and opening of obstructed Eustachian tubes.

Oral decongestants may cause hypertension, tachycardia, agitation, and insomnia. One advantage of oral decongestants is that they do not cause rebound congestion (rhinitis medicamentosa), which may be a consequence of the topical preparations.

### Antihistamines

Both oral and topical preparations of antihistamines are available without a prescription. Topical antihistamines (e.g. azelastine) are safe and have a rapid onset of action (~15 min), but don't affect co-morbid conditions such as conjunctivitis. Oral antihistamines, (e.g. loratadine) are also effective and have an onset of action ~1 hour. In contrast to topical antihistamines, oral antihistamines may reduce conjunctival and skin symptoms. Oral antihistamines are most effective when taken regularly, rather than on-demand, and, some subjects are sedated by the second generation antihistamines.

### Chromones

The chromones (e.g. cromolyn, nedocromil) block mast cell degranulation, and are also known as mast cell stabilizers. They are safe, but require several applications per day and are among the least effective of available agents for the treatment of AR.

### Anticholinergics

Topical anticholinergics (ipratropium bromide) are relatively safe, and affect only rhinorrhea. They require several applications per day, and may cause dry nose, epistaxis, glaucoma or urinary retention.

### Antileukotrienes

Antileukotrienes may either be receptor antagonists (montelukast) or inhibitors of leukotriene synthesis (zileuton). They are safe and effective, but there are occasional results of AE such as headache and gastrointestinal symptoms.

### Corticosteroids

Topical corticosteroids (fluticasone, mometasone, and others) are the effective anti-inflammatory agents that suppress all nasal symptoms and can affect conjunctival symptoms and enhance the quality of life. Reduction of symptoms does require long term use and often they are used incorrectly, which may result in treatment failure or epistaxis. Oral corticosteroids are used for rescue treatment, but are not indicated for long-term therapy for AR because of the well-known AE associated with systemic corticosteroid therapy.

## **2.3 Safety and Efficacy of Pharmacologically Related Products**

Currently, there are no products approved for SLIT in the US. Allergen immunotherapy is approved only for administration by SCIT—subcutaneous immunotherapy.

### *Subcutaneous Immunotherapy (SCIT) for the treatment of AR*

Immunotherapy involves the administration of gradually increasing doses of the allergen over a period of time to desensitize the subject. It is the only known treatment that modifies the immune response and treats the cause rather than the symptoms. In the US, the only licensed route of administration is subcutaneous injection (SCIT).

In November, 2011, the Laboratory of Immunobiochemistry reported to the Allergic Products Advisory Committee (APAC) a summary of safety data associated with SCIT. From submissions to the Adverse Events Reporting System (AERS) database, 195 adverse events after SCIT between 1987 and 2009 were reported, of which 43% were either “allergic” or “anaphylaxis,” and 19.4% of which resulted in hospitalizations. During this time period there have been 15 deaths, but significantly, no deaths have been reported due to SCIT in the years 2008-2011 (Epstein et al, *Ann Allergy Asthma Immunol* 110 (2013) 274e278). Severe asthma is a known risk factor for SAE and death due to immunotherapy. When administered by qualified and trained clinicians in the clinic setting, SCIT is considered safe and effective. Because of its discomfort, the risk of local and systemic allergic reactions, and the inconvenience of frequent injections, however, only 5% of US patients with allergic rhinitis, asthma, or both receive SCIT.

### *Sublingual Immunotherapy (SLIT) for the treatment of AR in the US vs. Europe*

There are no products approved for administration by SLIT in the US. A survey of European and American practices (Cox and Jacobsen, *Ann Allergy Asthma Immunol* 103:451; 2009) revealed that in 2009, 5.9% of allergists were prescribing SLIT. For this



“off-label” use, allergenic extracts prepared and FDA-approved for SCIT would be placed under the tongue (presumably) with a syringe. Worldwide, SLIT use is highly variable, and appears to be increasing.

The Cochrane Review of SLIT published in 2010 (Radulovic S., et al. Cochrane Database Syst Rev. 2010;12:CD002893) includes a meta-analysis of 60 randomized controlled clinical trials of SLIT, in which 2333 SLIT and 2256 placebo participants were studied. Symptom and medication scores were both improved, and in contrast to SCIT, none of the trials reported severe systemic reactions or anaphylaxis, and none of the systemic reactions that were reported required the use of epinephrine. When compared directly with SCIT, SLIT appeared to be associated with fewer SAE (summarized in Reference 8; AHRQ Publication No. 13-EHC061-EF). The combined experience, therefore, supports at least equivalent efficacy of SLIT compared to SCIT for ARC, and suggests that SLIT has a better safety profile.

Because SLIT is tolerated better than SCIT and can be self-administered at home, it is expected that subjects with immunotherapy who declined SCIT because of anticipated AE or the required commitment to physician office visits will elect to undergo immunotherapy with SLIT.

As stated in the Executive Summary of the AHRQ Publication, however, subjects included in clinical studies of SLIT included only subjects with ARC with or without mild asthma. “Hence, although it may appear . . . that sublingual immunotherapy may be safer than subcutaneous immunotherapy, the safety data from these subgroups of subjects *must not be extrapolated to the more severely affected subjects*” (emphasis added).

#### **2.4 Previous Human Experience with the Product (Including Foreign Experience) |**

##### *General summary of European experience with ORALAIR*

In 2008, Stallergenes was granted with authorization to market ORALAIR in Germany as a “named subject product,” an intermediate between investigational versus licensed status. It is not known how many German patients received the product between 2008 and November, 2012, when ORALAIR was granted European approval for treatment of adults and children in Canada, Germany and most of Europe including: Austria, Belgium, Bulgaria, Cyprus, the Czech Republic, Estonia, France, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, the Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, and Spain.

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

In a letter dated August 6, 2007, the sponsor’s representative requested a Type C meeting to discuss with CBER CMC and pre-clinical issues towards licensure of ORALAIR in the US for the treatment of ARC due to grass pollen sensitivity. Included with the request was a support document that included summaries of pharmaceutical development of the drug substance, the drug product, and the clinical development program.

On November 15, 2007, the Type C meeting took place in Rockville, MD. Pre-clinical and clinical issues were discussed. The pre-clinical issues were satisfied without requiring substantial additional interactions between the sponsors and CBER. CMC and clinical issues required additional interaction--either face-to-face or teleconference. Each of these CMC and clinical issues is addressed below with their own chronology of regulatory activity.

*CMC Issue 1: Validation that the drug substance includes appropriate levels of (b)(4)*  
(b)(4)

November 15, 2007 (face to face)

Stallergenes manufactures the five grass pollen extract by (b)(4)

(b)(4)

(b)(4)

(b)(4)

April 12, 2012 (face to face)

To address CBER's concern regarding characterization of the product, the sponsor proposed a (b)(4) method that demonstrates qualitative presence of all five grass pollen extracts in the final product. It was noted as well that the (b)(4) method does not quantitatively demonstrate that each of the pollen extracts are present in the proportions to which they are added to the mix. It was agreed that while an (b)(4) would be ideal for this purpose, the similarity of allergens among the five extracts is such that they may not be antigenically distinguishable.

The sponsor proposed a combination of methods to demonstrate the consistency of total allergenic activity and major allergen composition which included: (b)(4)

(b)(4)

In addition, the sponsor stated that the (b)(4)

(b)(4) Consequently, these allergens cannot be quantified separately within the drug substance. In view of these difficulties, the sponsor proposed to assure batch to batch consistency by (b)(4)

(b)(4)

(b)(4)

In closing, the sponsor agreed to provide an experimental study plan to address the relative contribution of the five individual grass pollens to the mix.

April 27, 2013 (IND 13776, Amendment 50)

The sponsor submitted a protocol entitled "Assessment of the contribution of individual grass pollens to the mix: Comparison between 5-grass pollen extracts" to compare the five pollen mixture with individual four pollen mixtures by (b)(4)

The (b)(4) will demonstrate that total allergenic activity is affected by omitting each of the five grasses from the mix. Specifically, (b)(4)

The (b)(4) will measure Group 5 allergen content with (b)(4)

The agency agreed with the proposed plan.

July 5, 2012 (IND 13776, Amendment 55)

Data from the proposed (b)(4) experiments outlined above were submitted to the agency. For the (b)(4), differences among the 5-grass mixture and each of the 4-grass mixtures were used to assign a value of contribution for each of the grass pollens. For example if the 5-grass mix has a total allergenic activity of 4245 IR/mL and a mix of 4 species in which Timothy grass pollen was omitted has an allergenic activity of 2683 IR/mL, then the contribution from Timothy pollen is  $4245 - 2683 = 1562$  IR/mL.

Similar comparisons were reported for the Group 5 allergen content with the (b)(4). Furthermore, the results of the (b)(4) correlated well. The detailed results of these studies may be found in the CMC review of the BLA.

It was reported in the review of this amendment that the data were acceptable, and that overall, the CMC data were acceptable for submission of a BLA.

*CMC Issue 2: Stallergenes' preference to describe potency according to an in-house reference*

November 15, 2007 (face to face)

CBER agreed that the regulations allow the sponsors to define potency of this particular product using their own units. Because this is an extract of five grass pollens, each of which are among those that CBER standardizes for potency, the product must also be described by the Bioequivalent Allergy Unit (BAU) standard. The manner in which IR

potency of the mixture will be converted to BAU that are currently used to define individual extracts was not clear and would require internal deliberation and additional conversations between the sponsor and CBER. CBER stated explicitly that this commercial characterization of the product should be complete by the beginning of the Phase 3 trials.

In July 17, 2008 memo the Agency requested of the sponsor to determine the potency in BAU/tablet with the US reference standards and to include BAU release specification for manufacturing consistency in addition to IR/tablet.

December 8, 2011 (Amendment 28)

In response to the agency's request, the sponsor submitted a report entitled "Relevance of using adapted BAU for ORALAIR drug product," in which the sponsor proposed maintaining labeling in IR without defining potency in BAU. The sponsor also suggested the possibility of developing an "adapted CBER assay" for the 5-grass mix drug product to determine potency in BAU.

This "adapted CBER assay" to determine "adapted BAU" used, for reference sera, pooled human serum aliquots from highly grass-allergic subjects. For the reference standard, the sponsor used a mixture of the five individual grass pollen reference extracts, which they termed the "in-house reference preparation" (IHRP). The IHRP is produced with the same method as is used to produce the drug substance, is analyzed by (b)(4) and was calibrated by testing on sensitive subjects with serial skin prick testing. The sponsor asserted that IR and "adapted BAU" correlate. CBER agreed with this assertion.

The sponsor also stated that because the drug is in tablet form rather than a liquid for injection, that BAU measurement of potency is irrelevant. CBER disagreed, and stated that the manufacturer must provide release specifications in both IR and BAU.

April 12, 2012 (Type C, face to face)

The firm agreed to measure total allergenic activity in BAU/tablet and requested reference reagents from CBER for this purpose. The Agency agreed to provide individual grass reference standards and its pooled reference serum to the sponsor.

October 25, 2012 (IND 13776, Amendment 66)

The sponsor provided data from two different studies performed using batches of 100 IR and 300 IR tablets. For reporting BAU release specification they combined data from both the studies and provided the release specification. These same release specifications were included in the BLA. Details of release specifications can be found in the CMC review.

November 26, 2012 (Agency Information Request)

CBER requested that the sponsor recalculate the BAU release specifications without pooling data from the two different studies outlined above. The request was reiterated during a teleconference March 20, 2013. The firm agreed to recalculate their (b)(4) to provide new BAU release specification for the 100 IR and 300 IR tablets.

April 30, 2013 (BLA 125471, Supplement 09)

In this supplement, the firm provided a detailed method of BAU calculation along with BAU/tablet release specifications for 100 IR and 300 IR tablets. As mentioned above, two different studies were performed. In the first study, the sponsor used their own (b) format and reference reagents. In the second study, the sponsor used CBER's plate layout (SOP 000152) and reference materials.

The sponsor also presented full calculations using CBER's Microsoft Excel calculation spreadsheet (SOP 000152). For the purposes of BLA review, the release specifications obtained from Study 2 are most relevant as this study was performed and calculated with CBER's standardization methods and reagents. Based on this study, the mean value and release specification from Study 2 are: shown in Table 2.

**Table 2. Release specifications, BAU/tablet, for ORALAIR**

	Mean BAU	Range of BAU
100 IR Tablets	(b)	(b)(4)
300 IR Tablets	(b)	(b)(4)

The Agency found these BAU/tablet release specifications acceptable.

*CMC Issue 3: Extrapolation of stability data from one grass pollen (orchard grass) to other pollens*

November 15, 2007 (face to face)

The sponsor asserted that it is valid to extrapolate data from the stability of orchard grass pollen extract towards the five-grass pollen extract mixture. CBER did not concur and stated that the sponsor must submit an alternative plan. In the BLA, the sponsors present stability data on four batches of the 5-grass extract drug substance. Details may be found in the CMC review of the BLA. The data and stability analysis plan are acceptable to the Agency.

*Clinical Issue 1: Dosage*

November 15, 2007 (face to face)

CBER agreed with the sponsor that the data suggested that a daily dosage of 500 IR was of no greater benefit than 300 IR, and that 100 IR each day was no better than placebo. CBER was not convinced that the sponsors had adequately addressed whether 500 IR/day is superior to 300 IR/day. The sponsor replied that while these doses are probably equally effective, Study VO34.04 demonstrated that the 500 IR dose is associated with a higher incidence of AE. CBER accepted 300 IR/day as the dosage to be used for US IND studies.

*Clinical Issue 2: Endpoint parameter for assessing proof of efficacy*  
September 23, 2009 (teleconference)

IND 13776 was submitted on 25 July 2008, and the US Phase 3 study, VO68.08USA commenced prior to GPS 2009, and was completed in autumn, 2009. During this time, however, there was ongoing discussion regarding the SAP, and the appropriate algorithm for calculating the primary endpoint. On June 25, 2009, the sponsors submitted a revised SAP.

For the primary endpoint, the sponsors proposed the AASS, which is a complex averaging system that was used for VO53.06, multiyear Phase 3 study performed in EU, Canada and Russia, and VO61.08, a single year Phase 3 study performed in the EU (See also Grouin, Vicaut, and Jean-Alphonse et al. *Clin Exp Allergy* 41:1282; 2011).

During this meeting the sponsor acknowledged that CBER had stated in October 2008, prior to commencement of the Phase 3 study, that CBER considered the AASS to be needlessly complex, and was not convinced by the sponsor's assertions that the AASS is the best parameter by which to measure clinical efficacy. It was clarified that the endpoint for Protocol VO68.08USA would be the combined score (CS), in which:

$$CS = (RTSS/6 + RMS)/2.$$

The RMS is the score of use of rescue medication and ranges from 0 to 3. The RTSS is the rhinoconjunctivitis total symptom score, in which each of six symptoms (sneezing, rhinorrhea, nasal pruritus, nasal congestion, ocular pruritus, and tearing) is scored from 0 to 3 and then averaged (sum of the six scores will range from 0-3, and the CS will range from 0-3. This change in primary endpoint parameter was agreed upon prior to data lockdown.

CBER agreed that this endpoint parameter is acceptable.

*Clinical Issue 3: Statistical differences between treatment and placebo groups required to meet proof of efficacy.*

May 12, 2011 Informational APAC meeting to discuss chamber studies to support effectiveness.

CBER Biostatistician Tammy Massie, PhD presented to APAC on May 12, 2011 a presentation entitled "Statistical Criteria for Establishing Safety and Efficacy of Allergenic Products," in which the lower bound of the 95% CI as a pre-specified threshold in this type of clinical trial was discussed.

As a consequence of discussion and public comments in response to APAC presentation by Dr. Massie on May 12, 2011 (available for review in the meeting transcript), CBER began a process of defining its statistical criteria to prove efficacy of allergenic products for immunotherapy. Ultimately CBER defined these criteria such that a 95% UL greater than 10% of the CS of the placebo group was considered acceptable.

June 10, 2011 (IND 13776, Amendment 21)

In this amendment the sponsor discussed the results of the Phase 3 Protocol VO61.08 USA, and included analyses of three European natural pollen exposure trials with this product.

The primary endpoint of VO61.08, however was stated in Amendment 8: “The study will be declared positive if the daily CS mean difference from the repeated measure ANCOVA model, between the active and placebo groups, is statistically significant ( $p \leq 0.05$  and 0 not included in the 95% CI of the mean difference from repeated measure ANCOVA), and inferior or equal to -0.14, which is considered clinically significant.”

CBER did not accept the criteria for the 95% CI of “0 not included in the 95% CI,” and initially inferred from the phrase “and inferior or equal to -0.14” that in fact the 95% CI LL must be superior to -0.14. Upon analysis of the data from Protocol VO61.08 USA, the point estimate of the difference in CS was -0.13, (-28.2%) with 95% CI LL of -0.06 (-13.0% of the placebo group CS). Therefore, the study did not meet its endpoints based on both the point estimate of the difference in CS, and the 95% CI of the point estimate.

This submission also included data from a multiyear European trial, VO53.06 (the comprehensive data for this trial were submitted in Amendment 31), which demonstrated efficacy in the first year of treatment with point estimate of the difference in the CS of -0.11 (-16.4%) and the 95% CI of -0.18, -0.04 (-27.0%, -5.8%). Data were stronger for the second and third years of therapy. The apparent difference in CS was maintained for the first post-therapy year (fourth year of study, observation only) but not the second post-therapy year.

The Clinical Trial Review of Amendment 21 stated that “The data support the safety of this product. Efficacy has not been proven to CBER’s satisfaction,” and suggested that a successful environmental exposure chamber trial may be useful towards support of a BLA application.

December 14, 2011 (CBER Letter)

This letter addressed all clinical submissions through November 7, 2011. The letter stated that the sponsors did not meet their clinical endpoints. The agency requested an additional field study or a chamber study could provide the necessary data to support efficacy. In response, the sponsors stated that such a chamber study had been performed in Vienna, Austria, and completed in 2008. CBER replied that this study may be used to support proof of efficacy.

March 19, 2012 (IND 13776, Amendment 45)

Data were submitted from the chamber study performed in Vienna, Austria in 2008. These data met the pre-specified endpoints (see Protocol VO56.07 summary, Section 6).

At this point, CBER had refined its statistical criteria for proof of efficacy. According to the refined criteria, while the point estimate of the difference in the CS in the US trial VO61.08 did not meet the primary endpoint, the 95% LL of VO61.08 of -13.0% was acceptable. In the context of the totality of the European clinical field studies as well as

the chamber study, CBER reviewers concluded that Stallergenes has provided sufficient clinical proof of safety and efficacy to move forward with a BLA.

April 11, 2012 (Type C, face to face)

CBER informed the sponsor that they have provided sufficient clinical proof of safety and efficacy to move forward with a BLA.

On August 24, 2012, CBER received a request for a pre-BLA meeting with a series of clinical and CMC-related questions. In general, the Agency concurred that clinical and CMC data support submission of a BLA. On November 15, 2012, a Type B Pre-BLA Meeting was held. On December 18, 2012, CBER received BLA 125471.0, and on February 14, 2013, BLA 125471.0 was filed.

Three issues were addressed during post-submission communications:

- 1: The Agency informed the sponsor that the lower age limit of patients for whom ORALAIR is indicated will be 10 years of age. The sponsor may conduct safety studies to enlarge the database of children 5-9 years of age.
2. In the BLA, the sponsors proposed that the initial dosing in adults is 300 IR. The sponsor then proposed to harmonize dosing of adults to that of children: 100 IR the first day, 200 IR the second day, and 300 IR thereafter. The Agency rejects this modification of the dosing schedule because the sponsors studied 300 IR dosing in adults without ramp-up; data therefore supports dosing in adults without ramp-up. Furthermore, when patients ramp-up the dose at home, the full dose of 300 IR is not taken under observation at the health care setting. Rather than, as the sponsor suggested, enhancing the safety profile of ORALAIR, ramp-up may increase the potential for unobserved AE, and diminish the safety profile of ORALAIR. Therefore, the agency denies the sponsor's request to modify the dosing regimen of ORALAIR for adults.

*Pediatric Requests*

The sponsors submitted data from Study VO52.06 to support use in children 5 years of age and older, and a partial waiver for use in children less than 5 years of age. The reviewer agrees with including children five years of age and older in the indications. The reviewer also agrees with the waiver of children less than five years of age. The basis for the waiver is that "studies are impossible or highly impractical," because the number of younger children with seasonal pollen allergy is quite small. The waiver is scheduled to be presented to the Pediatric Review Committee (PeRC) on March 19, 2014.

**2.6 Other Relevant Background Information** |

None

**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 or an unreasonable number of information requests.



### 3.2 Compliance With Good Clinical Practices And Submission Integrity |

A review was conducted by the Bioresearch Monitoring Branch of testing records, regulatory binders, study specific standard operating procedures, and general study conduct. In addition, source documents were reviewed and compared to the data tables submitted by the sponsor in the application. Two of the study sites were classified as “no action indicated,” as no significant objectionable conditions or practices were observed during the inspection, and a Form FDA 483 was not issued.

For a third study site, the inspection resulted in the issuance of a three item Form FDA 483 for Good Clinical Practice (GCP) violations, and received a final classification of “voluntary action indicated because for one subject, the medical records for the time period in which the subject was enrolled in the study were not available for review/audit. For the four of 23 subjects, the time of observation after administration of the Investigational Product (IP) was not documented; and for one subject, the Visit-6 blood samples were instead collected at Visit-7; for one subject, the medical records are not in enough detail to confirm the Visit-6 global evaluation. Furthermore, discrepancies in the diary for two subjects made the primary efficacy data points (sneezing for one subject, and runny nose for another subject) difficult to verify, illegible handwriting made it difficult to verify the weight of one subject between what was recorded in the Case Report Form and the medical record; and there is conflicting Visit-1 Skin Prick data recorded for two subjects.

Inspection of the fourth study site resulted in the issuance of a 2-part Form FDA 483. The following are the observations recorded:

- The number of investigational study drug tablets returned to the sponsor could not be verified for 11 subjects.
- Visit-4 compliance rate for one subject was reported to be less than 80% for taking the IP. The protocol requires a compliance rate of 80 to 120 percent.
- A pregnancy test was not performed for one female subject of child bearing potential during visit-4. The protocol requires a pregnancy test to be performed during Visit-4.
- Vital sign measurements for blood pressure and pulse rate were not performed for one subject during visit-4. The protocol requires that blood pressure and pulse rate measurements are performed during this visit.
- Two subjects were reported to have taken Nyquil during a period encompassing Visit-1 through Visit-7 of the study, and the Nyquil was not taken to treat an adverse event. The protocol specifies that treatments including antihistamines and decongestants are prohibited from Visit-1 up to Visit-7, unless used to treat an adverse event
- A pregnancy test was not performed for one female subject of child bearing potential during visit-4. The protocol requires a pregnancy test to be performed during visit-4.
- Vital sign measurements for blood pressure and pulse rate were not performed for one subject during visit-4. The protocol requires that blood pressure and pulse rate measurements are performed during this visit.

- Two subjects were reported to have taken Nyquil during a period encompassing Visit-1 through Visit-7 of the study, and the Nyquil was not taken to treat an adverse event. The protocol specifies that treatments including antihistamines and decongestants are prohibited from Visit-1 up to Visit-7, unless used to treat an adverse event.

**Clinical Reviewer Comment:** The violations of GCP recorded above do not significantly impact significantly on the assessment of the product’s safety and efficacy.

### 3.3 Financial Disclosures

On Form 3454, the sponsor certified that the following statement is correct: “As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).”

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

### 4.1 Chemistry, Manufacturing, and Controls

The drug substance is referred to by the sponsor as “5-grass pollen allergenic extract (b)(4) freeze-dried.” The drug product is a tablet comprised of the drug substance that is (b)(4), mixed with D-mannitol, and freeze-dried into tablets. The pollens are from five grass species.

**Table 3. Grass species of pollens that are extracted for the drug substance**

Extracted from original BLA 125471/0000, Table 2.3.S-1

<i>American common name</i>	<i>Latin name</i>	<i>English name</i>
Sweet Vernalgrass	<i>Anthoxanthum odoratum</i> L.	Sweet vernal grass
Orchardgrass	<i>Dactylis glomerata</i> L.	Cocksfoot
Perennial Ryegrass	<i>Lolium perenne</i> L.	Ryegrass
Timothy	<i>Phleum pratense</i> L.	Timothy
Kentucky Bluegrass	<i>Poa pratensis</i> L.	Meadow grass

Clinically relevant CMC issues were discussed in Section 2.5, “Summary of Pre- and Post-submission Regulatory Activity Related to the Submission.”

### 4.2 Assay Validation

The sponsor’s choice to (b)(4) impacts potency assay validation. In the original BLA submission, the sponsor planned to assay for potency using (b)(4)

(b)(4)

As stated during a teleconference on March 20, 2013, CBER was concerned that its own 5-pollen extract mixture will be unable to precisely replicate the sponsor's product. If there are differences between the pollen species that CBER chooses as the (b)(4) and the sponsor's mixed pollen (b)(4), the consequent differences between CBER's and the sponsor's measurements of may have two potential adverse outcomes: First, there may be a delay of BLA approval. Second, there may be subsequent errors in validation of the sponsor's potency measurements which will result in rejection of lot release into the US.

CBER addressed this concern by requesting that because these five grass pollen extracts are highly cross-reactive, the final potency assays shall use a single representative allergen extract as the (b)(4). Use of the most cross-reactive species as the (b)(4) is expected to be more reproducible (among the two laboratories performing the assay) than use of a mixture.

To determine which individual extract may best represent the mixture for potency measurements, CBER requested that the sponsor run individual (b)(4) assays against individual extracts of each of the five pollens as the (b)(4) against the manufacturer's product (in solution). The manufacturer performed the assays with (b) different lots of product and sent the results to CBER on July 17, 2013. )

Each of the sets of assays was highly reproducible, and CBER decided that because Timothy grass sensitivity was the primary inclusion criterion for the US study, that Timothy grass pollen allergen extract would be used as the (b)(4) to measure potency in BAU. In January 2014, the Sponsor submitted to the Agency samples from three lots of ORALAIR for validation of potency testing. CBER tested the samples in March, 2014; and the results of this testing shown in Table 4 demonstrate validate the potency sponsor's potency measurements.

**Table 4. Potency validation of samples from three lots of ORALAIR**

Lot number	Sponsor's potency measurement	CBER's potency measurement	Potency Validated by CBER
(b)	1.01	1.06	Yes
(b)	1.00	1.14	Yes
(b)	1.00	1.00	Yes

#### **4.3 Nonclinical Pharmacology/Toxicology**

Repeat-dose toxicity, genotoxicity, reproductive and developmental toxicity and local tolerance studies have been performed on this product. For a full analysis of these studies, please refer to the toxicology review.

Studies of potential effects by this product were first performed on embryo-fetal development were performed with 30 mated (b)(4) rabbits, 18-20 weeks

old who received up to 1000 IR/kg/day of this product between GD6 to GD18. There were no indications of maternal or fetal toxicity in this supportive study.

The pivotal study was performed in 24 mated female rats, 11 weeks old, who received up to 1000 IR/kg/day for 12 days, between GD6 to GD17. Terminal examination was performed on GD21. There was no evidence of maternal or fetal toxicity of this product in this pivotal study.

#### **4.4 Clinical Pharmacology** |

No clinical pharmacology studies were performed, and in general, are not relevant to this class of product.

##### 4.4.1 Mechanism of Action |

Independent of route, allergen immunotherapy is a therapeutic vaccination intended to re-orient the immune response away from the production of allergen-specific IgE antibodies and towards either desensitization or tolerance of the allergen (temporary or permanent state of no immune response) or towards a different immune response that generates a different class of antibodies. The mechanisms by which the immune response is reoriented are incompletely understood, and may differ among a heterogeneous population of humans. Descriptions of these mechanisms of allergen immunotherapy are beyond the scope of this document.

##### 4.4.2 Human Pharmacodynamics (PD) |

Human PD studies were not performed, and in general are not relevant to allergenic immunotherapy.

##### 4.4.3 Human Pharmacokinetics (PK) |

Human PK studies were not performed, and in general, are not relevant to this form of therapy.

#### **4.5 Statistical** |

The statistical reviewer analyzed efficacy and safety/tolerability datasets provided by the applicant in this submission. Analysis of the primary study endpoints, select relevant secondary endpoints and the safety/tolerability data included in this submission were verified to be consistent with the sponsor's results. The data analysis was performed utilizing SAS version 8.2 and/or JMP Version 9 and was based upon the pre-specified Statistical Analysis Plan (SAP) incorporating appropriate models proposed by the sponsor. In the case of studies performed under US-IND the Statistical Analysis Plan and models associated with primary and secondary endpoints were explicitly agreed to by the Agency. The results of the statistical analysis were confirmed independently by the reviewing statistician and illustrate the safety/tolerability and efficacy of this sublingual grass immunotherapy product.

#### **4.6 Pharmacovigilance**

The Pharmacovigilance plan was submitted in STN 125471\0\1 (Supplement 1), and was reviewed in a document submitted to the file on June 10, 2013 by Dr. Patricia Rohan. The sponsor proposes to continue routine Pharmacovigilance in accordance with ICH Guidance E2E. Expedited AE and periodic safety reports will be submitted to FDA. These events are subject to enhanced surveillance: allergic reactions including severe laryngopharyngeal disorders, autoimmune disease, and anaphylaxis. CBER agrees with the proposed plan.

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

#### **5.1 Review Strategy**

The BLA application and clinically relevant supplements were the primary source of information for this review. As indicated, tables and figures have been copied and pasted from the original BLA into the clinical review. The clinical reviewer also referred to documents from IND 13776 (including clinical trial outlines and reports) and publications listed in Section 5.5.

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

The source of clinical data used for review is BLA submission, including the final study reports contained within the submission. Most of the data that support this submission are found in Module 5 of the original submission of BLA 125471.

In addition to the BLA submission, the reviewer referred to reviews of IND submissions, the submissions themselves, and CBER memos including minutes of teleconferences and face-to-face meetings with the sponsor.

Protocol VO61.08USA tested the safety and efficacy in an adult cohort, 18-65 years of age, in the US and was pivotal to support licensure of ORALAIR in the US. Protocol VO52.06 was a Phase 3 study of children and adolescents, 5-17 years of age, which was performed in the EU, and is pivotal for licensure of ORALAIR to treat subjects within this age group.

The following protocols studied adult subjects from 18 years to either 50 or 65 years of age. Protocol VO34.04 was considered supportive for choice of dose, safety and efficacy. Protocol VO56.07 was performed in an environmental exposure unit, and is supportive for safety and efficacy.

Protocols VO53.06 and VO60.08 were Phase 3 studies performed in the EU and are supportive for safety. Protocol VO60.08 treated subjects with ORALAIR for two months (rather than four) prior to the GPS, and did not demonstrate efficacy. Protocol VO53.06 studied the effects of administration of ORALAIR for three successive years, and for efficacy during GPS beyond the third treatment year. Therefore, Protocol VO53.06

supports claims that use of ORALAIR for three consecutive years is safe, and that efficacy persists for at least one year after treatment is discontinued.

Protocol VO40.05 was an extension of VO34.04 that was discontinued because German and French regulatory authorities had issues with product quality that were subsequently satisfactorily addressed; no study drug was administered and Protocol VO40.05 is not reviewed in this document. Protocol VO33.04DK was considered supportive for safety, but is a small trial that adds no critical information, and thus is not reviewed in this document.

### 5.3 Table of Studies/Clinical Trials

Studies shaded in light gray were not reviewed for this document.

**Table 5. Clinical Studies included in original BLA submission for ORALAIR (5-grass pollen extract) sublingual tablet**

Adapted from original BLA 125471/0000, Module 2.5, Table 2.5-1, Pages 9-11 of 132

Protocol #	Completion status Year/pollen season	Location	Phase of Study	Study design, & objectives	Study population* Age range	Treatment doses & schedule	Number of exposed subjects	Treatment duration	Study Endpoint Parameter	Outcome of Study
VO33.04 DK	2004 Out of the pollen season	EU	1/2a	DBPC, randomized, single center safety	18–50y	100 IR to 500 IR Placebo Dose escalation or Direct administ.	23 <sub>b,d</sub> 7 <sub>c,d</sub>	10 days	safety	no unexpected, severe, or serious safety signals
VO34.04	2005	EU	2b/3	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-season	ARTSS	300 and 500 IR dose different from placebo and about equal to each other; ~40% improvement, lower 95% CI 10.7-14.0%.
VO40.05	Early term. 2006	EU	3	DBPC, randomized, multi-national multicenter Post-treatment efficacy, Safety (Extension of VO34.04)	18-46y	300 IR (4M) Placebo Dose escalation	68 25	~4 month pre-season and ≥ 1 month co-season	ARTSS	terminated early; no data
VO52.06	2007	EU	3	DBPC, randomized, multi-national multicenter Efficacy, Safety	5-17y	300 IR (4M) Placebo Dose escalation	139 139	~4 month pre-season and ≥ 1 month co-season	ARTSS	Tx 25.4% better than placebo (lower 95% CI 10%);

Protocol #	Completion status Year/pollen season	Location	Phase of Study	Study design, & objectives	Study population* Age range	Treatment doses & schedule	Number of exposed subjects	Treatment duration	Study Endpoint Parameter	Outcome of Study
VO53.06	2007 2008 2009 2010 2011	EU, Canada Russia	3	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-season over 3 yrs	AASS	Each dose regimen effective; see full description
VO56.07 A	2007-2008 Out of the pollen season	EU	1	DBPC, randomized, mono-center (allergen exposition chamber study) Efficacy, Safety	18-50y	300 IR Placebo Direct administration	45 44	~4 months	ARTSS	28.7% improvement treatment vs. placebo in environmental chamber; lower 95% CI 14.2%
VO60.08	2009	EU	3	DBPC, randomized, multi-national multicenter Efficacy, Safety	12-65y	300 IR (2M)    Placebo Direct administration	188 (173 ≥ 18 years of age)  15 < 18 years of age)  193 (174 ≥ 18 years of age)  19 < 18 years of age)	~2 month pre-season and ≥ 1 m co-season	AASS	2-month pre-and co-seasonal regimen ineffective;
VO61.08 USA	2009	USA	3	DBPC, randomized, multicenter Efficacy, Safety	18-65y	300 IR (4M) Placebo Direct admin	233 240	~4 months pre-season and ≥ 1 monthco-season	CS	28.2% improvement (lower 95% CI, 13.0%)

\* Subjects with grass pollen ARC unless stated otherwise

A = Austria, DK = Denmark, EU = Europe, DBPC = Double-blind placebo-controlled, IR = Index of reactivity, SLIT = Sublingual immunotherapy, 4M = subjects received active treatment starting 4 months prior to the pollen season.

a Study code VOXX.YY definition: VO = Voie Orale (i.e., oral route in French) + XX = chronological study number + YY = Year of study implementation

b Subjects who received active treatment in Groups 1, 2, 3 and 4.

c Subjects who received placebo in Groups 1, 2, 3 and 4.

d Group 1: 6 subjects received a daily sublingual dose of 100 IR (Days 1 and 2), 200 IR (Days 3 and 4), 300 IR (Days 5 and 6), 400 IR (Days 7 and 8) and 500 IR (Days 9 and 10) and 2 subjects received placebo.

Group 2: 6 subjects received a daily sublingual dose of 100 IR on Day 1, 200 IR on Day 2, 300 IR on Day 3, 400 IR on Day 4 and 500 IR on Days 5 to 10 and 2 subjects received placebo.

Group 3: 6 subjects received a daily sublingual dose of 300 IR on Days 1 to 10 and 1 subject received placebo.

Group 4: 5 subjects received a daily sublingual dose of 500 IR on Days 1 to 10 and 2 subjects received placebo.

e Depending on the start and duration of the pollen season and the planned visit date.

e Depending on the start and duration of the pollen season and the planned visit date.

f Sustained efficacy is defined as maintenance of significant and clinically relevant efficacy during two to three treatment years [EMA, 2008].

e Depending on the start and duration of the pollen season and the planned visit date.

## 5.4 Consultations |

[There were no consultations external to the BLA review team.

### 5.4.1 Advisory Committee Meeting |

[This BLA was presented to the Allergenic Products Advisory Committee (APAC) on December 11, 2013. APAC concluded that ORALAIR is effective for grass pollen-induced allergic rhinitis or conjunctivitis in persons 5-65 years of age, when administered prior to and during the grass pollen season.

APAC considered whether ORALAIR is safe for young children because the tablet may require as long as one minute to dissolve. Some members of APAC were concerned that young children may swallow fragments of the tablets, and that swallowed tablet fragments may exacerbate inflammation in the esophagus and trigger eosinophilic esophagitis (EE). After discussion of this issue, APAC voted on whether ORALAIR is safe for children ages 5-9. The vote was 5 yes, and 5 no. At least two members of the committee explained that their vote was prompted by absence of data addressing the question of EE rather than a specific safety signal in the data.

There was also discussion about the ramp-up of dosing (100 IR the first day, 200 IR the second day, and 300 IR the third day). Some members of the committee questioned whether the ramp-up should be more gradual and extended over multiple days. Dr. Marianna Castells, however, asked whether it is safer to give the full dose on the first day, while the patient was being observed (see Transcripts to APAC meeting, Page 194)

APAC then voted on whether ORALAIR is safe and effective for children 10-17 years of age and for adults 18-65 years of age. The vote was 10-0 yes.

APAC then addressed the question of sustained efficacy. There was no vote, but the discussion indicates that the committee was not persuaded that efficacy lasted for an additional fourth year and fifth year after three years of ORALAIR.

APAC had reservations regarding safety, including the following:

1. Because of concern regarding swallowed tablet fragments inducing or unmasking eosinophilic esophagitis (discussed above), the committee recommended approval for children and adults ages 10-65.
2. APAC was concerned about life-threatening local and systemic allergic reactions, and therefore recommended that patients who are prescribed ORALAIR also must be prescribed auto-injectable epinephrine.
3. APAC was of the opinion that data on subjects >65 years of age were lacking. During this discussion, the sponsors agreed to a limit of upper age of 65 years of age in the product indications.
4. APAC suggested the post-marketing studies in the following sets of subjects to define more clearly safety and/or efficacy:
  - a. Adults > 65 years of age (primarily safety)
  - b. Children 5-10 years (for safety and efficacy)
  - c. Children and adults with moderate to severe asthma



- d. Children and adults with food allergy
- e. Racial or ethnic subpopulations (e.g. African-American, Hispanic)
- f. Monitor patients who have gastrointestinal symptoms for eosinophilic esophagitis and related diseases.
- g. Efficacy on subjects who are sensitive to additional environmental allergens (e.g. ragweed, trees)
- h. Safety for those receiving concomitant SCIT

#### 5.4.2 External Consults/Collaborations |

None

#### 5.5 Literature Reviewed |

The clinical reviewer consulted the literature and refers in the text to the following reports:

1. Radulovic S., Calderon M. A., Wilson D., Durham S. Sublingual immunotherapy for allergic rhinitis. *Cochrane Database Syst Rev.* 2010;12:CD002893
2. Bousquet J, Schunemann HJ et al. Allergic Rhinitis and its Impact on Asthma (ARIA): Achievements in 10 years and future needs. *J Allergy Clin Immunol* 130:1049; 2012
3. Greiner N and Hellings PW et al. *The Lancet* 178:2112; 2012
4. Cox L and Jacobsen L, *Ann Allergy Asthma Immunol* 103:451; 2009
5. Cox L and Nelson H et al. Immunotherapy practice parameters of the American Academy of Allergy, Asthma, and Immunology [AAAAI] *J Allergy Clin Immunol* 127:S1; 2011
6. Burks, WA, Calderon MA et al. Update on allergy immunotherapy: American Academy of Allergy, Asthma & Immunology/European Academy of Allergy and Clinical Immunology/PRACTALL consensus report. *J Allergy Clin Immunol* 131:1288; 2013
7. Passalacqua G and Baena-Cagnani CE et al. Grading local side effects of sublingual immunotherapy for Respiratory allergy: Speaking the same language. *J Allergy Clin Immunol* 132:93; 2013
8. Lin Sy, Erekosima N, Suarez-Cuervo C, Ramanathan, M, Kim JM, Ward D, Chellandurai Y, and Segal JB. Allergen-Specific Immunotherapy for the Treatment of Allergic Rhinoconjunctivitis and/or Asthma: Comparative Effectiveness Review. Effective Health Care Program Comparative Effectiveness Review Number 111, Agency for Healthcare Research and Quality; March 2013

The following reports specific to this BLA were consulted:

9. Juniper EF and Guyatt GH. Development and testing of a new measure of health status for clinical trials in rhinoconjunctivitis. *Clin Exp Allergy* 21:77; 1991
10. Grouin JM, Vicaut E et al. The average Adjusted Symptom Score, a new primary efficacy end-point for specific allergen immunotherapy trials. *Clin Exper Allergy* 41:1282; 2011
11. Hong J and Bielory L. Oralair<sup>®</sup>: sublingual immunotherapy for the treatment of grass pollen allergic rhinoconjunctivitis. *Expert Rev. Clin. Immunol.* 7:437; 2011
12. Horak F and Ziegelmayer P. Early onset of action of a 5-grass-pollen 300-IR sublingual immunotherapy tablet evaluated in an allergen challenge chamber. *J Allergy Clin Immunol* 124:471; 2009
13. Didier A and Margitta Worm M. Sustained 3-year efficacy of pre- and coseasonal 5-grass-pollen sublingual immunotherapy tablets in subjects with grass pollen-induced rhinoconjunctivitis. *J Allergy Clin Immunol* 128: 559; 2011

## 6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS |

### *General concepts regarding safety and anticipated AE*

In order to comprehend the review strategy and interpret the data that support safety of allergen immunotherapeutics, it is necessary to understand the AE that are anticipated with this class of products.

Allergen immunotherapy is essentially a therapeutic vaccination that currently consists of administration of an extract of the allergen to which an individual is sensitive in order to either desensitize (temporary and dependent on continued therapy) or tolerize (permanent loss of sensitization) the subject to the allergen. By definition, therefore, the drug substance is at least a component of the offending substance, and consequently, the AE that are expected to occur are those associated with allergic responses.

In general, allergic responses to administration of an allergenic extract are either local or systemic, or both. Local allergic responses to SCIT are centered on the injection site and include redness, swelling, itching and pain. Because the SCIT injection site is on the upper arm, there is little danger that the local reaction may be serious or life threatening.

Local allergic responses to SLIT include redness, swelling, itching and pain around the lips and throat, but may also include swelling of the uvula and hoarseness, and because some of the extract is swallowed, symptoms related to the gastrointestinal system such as abdominal pain and diarrhea. By contrast to SCIT, the anatomic nature of SLIT is such that local swelling (of the uvula or within the larynx) may obstruct the airway. There were no serious or life-threatening local events during the clinical trials with ORALAIR.

Systemic reactions are not uncommon with SCIT, occurring in up to 5% of subjects during the course of therapy. Most systemic reactions are mild or moderate and consist of generalized itching with or without hives, cough, or mild exacerbations of asthma. Rarely, systemic reactions may include severe asthma exacerbations and anaphylactic

shock, both of which may be fatal. When administered by a trained health professional, these SAE are very rare. SLIT, on the other hand, is associated with fewer systemic reactions, and life-threatening SAE after SLIT are exceedingly rare to date (e.g. four SAE in > 80,000 subject years of administration in Europe). In addition to convenience of home administration of SLIT, it has been proposed in the literature that a lower level of risk adds an advantage to SLIT over SCIT (for review, see the immunotherapy practice parameters of the American Academy of Allergy, Asthma, and Immunology [AAAAI] *J Allergy Clin Immunol* 127:S1; 2011). During review of this BLA, the World Allergy Organization proposed a harmonized grading system for local side effects of SLIT (Reference #6 in Section 5.5), which will be adopted for review of safety of this product.

*Relevant study parameters, variables, and endpoints to demonstrate efficacy of allergenic extracts for desensitization to environmental allergens*

In order to interpret the data that support efficacy of allergen immunotherapeutics, it is necessary to understand the unique variables associated with allergy to environmental substances, and in particular, to seasonal allergens.

By definition, natural exposure to seasonal allergens is dependent on region. Birch pollen, for example, is the major tree allergen in Northern Europe, while olive tree pollen is most important in Southern Europe. Ragweed is found throughout North America, but not in Europe. Grass pollens, particularly Timothy grass, are present in Europe and North America.

While the season in which these pollens are most prevalent is relatively constant within a region (e.g. tree pollen season is late winter/spring, grass pollen season is late spring/summer) the onset and end of each season varies and among regions. In addition, weather patterns that vary from year to year (rainfall for example) will in turn cause pollen levels to vary within the same region. Since the magnitude of symptoms in any allergic individual varies with these pollen levels, the severity of allergic disease experienced by that individual varies from year to year. Consequently, this variability impacts adversely on the ability to measure the efficacy of therapy among regions, and among years in the same region. These variables also impact upon the comparison within individual study subjects of their level of illness between a baseline and treatment season; paired data may be confounded by a high pollen season the first (baseline) year and low the next (treatment) year or vice versa.

Similar to many autoimmune and auto-inflammatory diseases, there is not one clinical parameter that serves as an index of disease severity. Furthermore complicating measurement of allergenic therapeutics, even though allergen-specific IgE mediates these allergic symptoms, serum levels of IgE cannot serve as a biomarker for response to therapy. The lack of any biomarker requires clinical scoring of symptoms, medication usage, or both (so-called combined scoring) as a primary endpoint. These measurements obviously are not ideal because clinical scores include some element of subjectivity, and therefore contribute to variability and to the statistical complexity of these studies.

There are multiple clinical scoring algorithms that may be used to demonstrate proof of efficacy of immunotherapy. Some of these consider only symptoms or quality of life, some consider medication usage, and some take both symptoms and medication usage into account. Clinical scores used by the sponsor to support proof of efficacy of ORALAIR and the method by which they are calculated are shown in Table 1. Of these, CBER considers the Average Combined Score (ACS) to be the best measure of therapeutic efficacy.

**Table 6. 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*	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**	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%

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

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

Using these scores (primarily the ACS), CBER considers data from natural exposure pollen studies (also referred to as “field trials”) as demonstrative of clinically meaningful efficacy if the reduction in clinical scores by therapy is greater than 15% of placebo AND the 95% lower confidence limit of that reduction is greater than 10% of the placebo scores.

### **6.1 Trial #1 (Supportive for safety and efficacy in adults with ARC)**

*Protocol VO34.04: Randomized, double-blind, placebo-controlled, multinational, multicenter, Phase 2b/3 study of efficacy and safety of three doses of sublingual immunotherapy administered as tablets once daily to subjects suffering from grass pollen rhinoconjunctivitis.*

#### 6.1.1 Protocol VO34.04 Objectives (Primary, Secondary, etc)

The Primary Objective was to assess the efficacy of SLIT on the Rhinoconjunctivitis Total Symptom Score (RTSS) of the six rhinoconjunctivitis symptoms: sneezing, rhinorrhea, nasal pruritus, nasal congestion, ocular pruritus and watery eyes.

The Secondary Objectives were to assess the efficacy of SLIT on the:

- rescue medication usage (use of antihistamine, nasal corticosteroids and systemic corticosteroids),
- six individual symptom scores of the Rhinoconjunctivitis Symptom Score (RSS),
- overall Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) score and
- global evaluation by the subject;

An additional Secondary Objective was to document the safety of the treatment.

Exploratory Objectives were to assess the efficacy of SLIT on the:

- Combined Score – a score taking into account the RTSS and rescue medication usage,
- Skin Prick Test (SPT) and immunological markers (serum-specific immunoglobulin E [IgE] and immunoglobulin G4 [IgG4]).

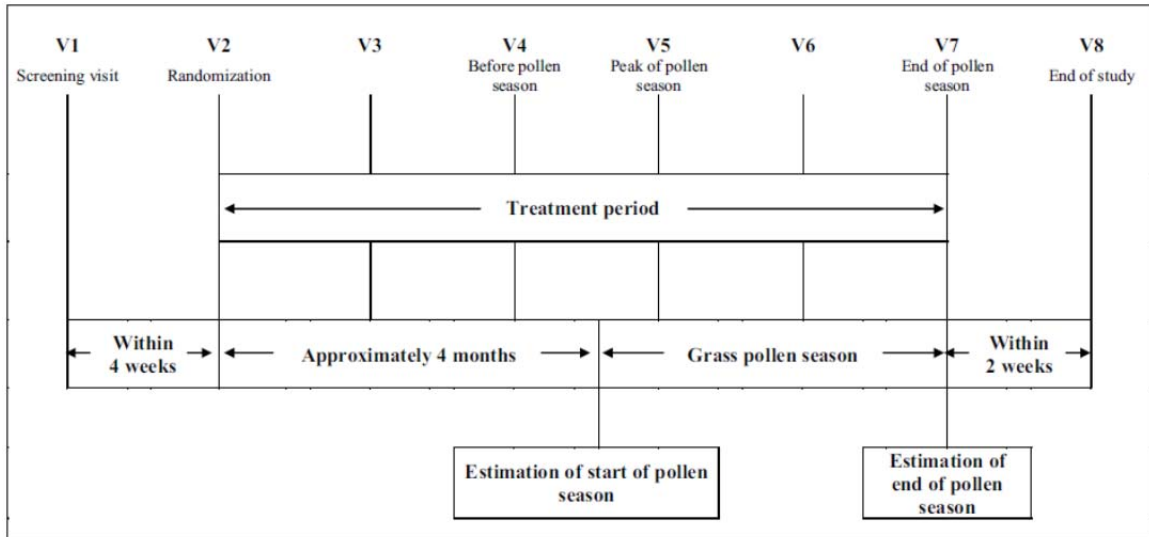
#### 6.1.2 Protocol VO34.04 Design Overview

Protocol VO34.04 was a DBPCR multi-national, multicenter (44 sites, 10 European countries) study of safety and efficacy that compared three doses of ORALAIR with placebo (4 groups, approximately 160 subjects in each group). Subjects were 18-45 years of age and were treated with 100 IR, 300 IR, or 500 IR of ORALAIR for four months prior to grass pollen season, and at least one month during the grass pollen season.

In this study, those who received 300 IR or 500 IR, first went through a ramp-up phase in which they took 100 IR the first day and increased the dose by 100 IR each day until the final randomized dose of either 300 IR or 500 IR was reached.

**Figure 1. Study Design, Protocol VO34.04**

From BLA 125471/0000, Clinical Study Report VO34.04 p22



*Reviewer comment:* The study was well designed to test differences in safety and efficacy among three doses of study drug. The study demonstrated that the 300 IR and 500 IR dose had greater efficacy than the 100 IR dose. The 500 IR dose was associated with more AE and did not demonstrate superior efficacy to the 300 IR dose. Therefore, the 300 IR dose was chosen for subsequent clinical trials. The reviewer agrees with the safety and efficacy assessments of Protocol VO34.04.

6.1.3 Protocol VO34.04 Population

Eligibility was restricted to adults 18 to 45 years (inclusive) who were suffering from seasonal grass pollen-related allergic rhinoconjunctivitis for at least 2 years (as confirmed by positive radioallergosorbent test [RAST] and SPT) with a score of at least 12 on the Retrospective Rhinoconjunctivitis Total Symptom Score (RRTSS). The subjects were otherwise healthy as determined by medical history, physical examination and safety laboratory tests. Subjects with asthma that required daily control (i.e. beyond “mild” severity) were excluded.

6.1.4 Protocol VO34.04 Study Treatments or Agents Mandated by the Protocol

6.1.5 Protocol VO34.04 Directions for Use

One tablet, place for one minute under the tongue before swallowing.

6.1.6 Sites and Centers

Protocol VO34.04 was conducted at 44 centers in 10 European countries. The first subject was screened on 30 November 2004 and the last subject completed the study on 05 September 2005.

#### 6.1.7 Surveillance/Monitoring

Safety assessments included a medical history profile at screening, physical examination (including vital signs) at Visit 1 (screening) through Visit 8 (end of study), AE monitoring throughout the study and assessment of routine safety laboratory tests at Visit 1 and Visit 7. Safety was monitored by an independent DSMB.

Subjects were monitored with a CRF for each visit, and kept diary cards between visits. They were given the opportunity to spontaneously report AE throughout the study, and a general prompt was also given to detect AEs (“Did you notice anything unusual about your health since your last visit?”).

In November, 2005, the DSMB met and determined, based on highly statistically significant difference between the 100 IR Group versus the 300 IR Group, and no significant difference between the 300 IR Group versus the 500 IR Group (p values = 0.0015 and 0.6082 respectively), that the 300 IR dose should be chosen for further investigation

#### 6.1.8 Protocol VO34.04 Endpoints and Criteria for Study Success

The primary efficacy endpoint was a difference in the RTSS that was recorded daily from Visit 4 (last visit before onset of grass pollen season) to Visit 8 (end of study).

The secondary efficacy assessments included the individual RSS, the Rhinoconjunctivitis Quality of Life Questionnaire, and a global evaluation of the efficacy of SLIT was made by subjects at Visit 7 and noted relative to the previous pollen period.

Safety assessments included a medical history profile at screening, physical examination (including vital signs) at Visit 1 through Visit 8, AE monitoring throughout the study and assessment of routine safety laboratory tests at Visit 1 and Visit 7.

#### 6.1.9 Protocol VO34.04 Statistical Considerations & Statistical Analysis Plan

The study tested the hypothesis that the RTSS over the grass pollen season would be no different in any of the three treatment groups (100 IR, 300 IR, or 500 IR daily) compared to the placebo group.

From previous study results, Stallergenes S.A. found that a sample size of 137 subjects per treatment group would have a power of 90% to detect a mean difference of 0.81, that is a difference of 0.2025 per symptom ( $0.81 / 4$ ), between Placebo and 300 IR in the mean Total Symptom Score (TSS) per 24 hours, assuming an overall  $\alpha$  of 0.05 and a common SD of 2.1. Assuming a 10% drop-out rate, it was decided to use 150 subjects in each of four treatment groups, resulting in a total of 600 evaluable subjects. Please refer to the statistical review for details and validation of the power analysis.

Where any of the six individual symptom scores for a given day was missing, the RTSS for that day was considered missing. Average RTSS scores were calculated using the non-missing data in the respective period. Missing data in the RQLQ was handled by using the worst case scenario. No other imputation of missing values was performed.

Please refer to the Statistical Review for more information.

#### 6.1.10 Protocol VO34.04 Study Population and Disposition

##### 6.1.10.1 Protocol VO34.04 Populations Enrolled/Analyzed

**Safety Population:** included all subjects who received at least one dose of investigational product.

The Intent-to-treat Population included all subjects who received at least one dose of investigational product and had a RRTSS and at least one RTSS in the pollen period while on treatment.

The Per Protocol Population (PP) included all subjects who completed the study according to the protocol and had no major protocol violations. Subjects had to qualify for inclusion in the ITT population in order to be included in the PP population. Subjects that were withdrawn from the study due to lack of efficacy or an investigational product-related AE, were included in the PP population if they were otherwise valid.

The number of subjects from each dose group that were included in the Safety, ITT and PP populations is shown below.

**Table 7. Populations enrolled and analyzed in Protocol VO34.04.**

From original BLA 125471/000; Clinical Study Report VO34.04, p.55

	<b>100 IR</b>	<b>300 IR</b>	<b>Year 3</b>	<b>Year 4</b>	<b>Year 5</b>
<b>Safety Population</b>	<b>157</b>	<b>155</b>	<b>160</b>	<b>156</b>	<b>628</b>
<b>Intent to treat</b>	<b>142</b>	<b>136</b>	<b>143</b>	<b>148</b>	<b>569</b>
<b>Per Protocol</b>	<b>132</b>	<b>123</b>	<b>133</b>	<b>136</b>	<b>524</b>

There were 59 subjects who did not record RTSS on each day of the pollen period, 37 of which withdrew from the study before the pollen period started and 22 who didn't complete the diary card correctly. There were 68 subjects without at least one RTSS in the worst pollen period. There were 17 subjects with major violations of prohibited drugs, and 17 who withdrew due to AE.

##### 6.1.10.1.1 Protocol VO34.04 Demographics

There was a somewhat unequal distribution of male and female subjects in the different study groups (see Table 8, below). The age, weight, height, and BMI among each of the treatment groups (100 IR, 300 IR, 500 IR or placebo) and each of the three study populations were equivalent (CSR VO34.04, Table 11-1, p 59).



**Table 8. Demographics of subjects in Protocol VO34.04.**

From original BLA 125471/000; Clinical Study Report VO34.04, p.58

	Safety Set n	Safety Set (Percent)	Intent to Treat n	Intent to Treat (percent)	Per Protocol n	Per Protocol (percent)
100 IR	157	(100.0)	142	(100.0)	132	(100.0)
100 IR Female	74	(47.1)	69	(48.6)	62	(47.0)
100 IR Male	83	(52.9)	73	(51.4)	70	(53.0)
300 IR	155	(100.0)	136	(100.0)	123	(100.0)
300 IR Female	70	(45.2)	62	(45.6)	57	(46.3)
300 IR Male	85	(54.8)	74	(54.4)	66	(53.7)
500 IR	160	(100.0)	143	(100.0)	133	(100.0)
500 IR Female	62	(38.8)	54	(37.8)	51	(38.3)
500 IR Male	98	(61.3)	89	(62.2)	82	(61.7)
Placebo	156	(100.0)	148	(100.0)	136	(100.0)
Placebo Female	60	(38.5)	60	(40.5)	57	(41.9)
Placebo Male	96	(61.5)	88	(59.5)	79	(58.1)
All	628	(100.0)	569	(100.0)	524	(100.0)
All Female	266	(42.4)	245	(43.1)	227	(43.3)
All Male	362	(57.6)	324	(56.9)	297	(56.7)

*6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population*

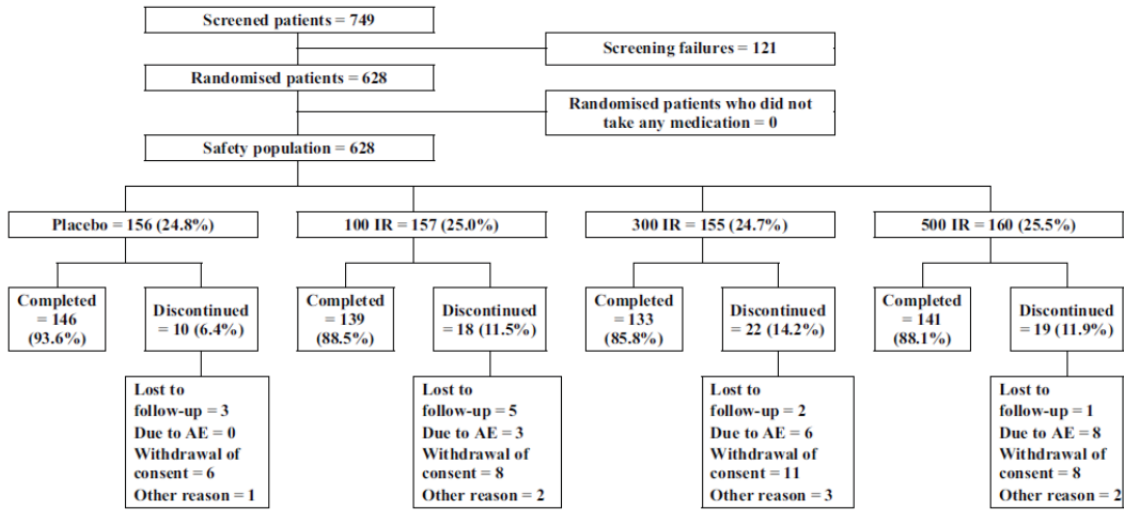
The subjects enrolled had ARC due to grass pollen sensitivity. Subjects were required to have symptoms due to seasonal allergic rhinitis due to grass pollen allergy, and otherwise in general good health. The distribution among subjects in each dose group for use of drugs unrelated to ARC was equivalent between treatment groups.

One major variable that may affect efficacy and safety are whether the subject has asthma. Only asthmatic subjects with FEV1 > 80% of normal and who are not taking daily medication for asthma were randomized. Each study group included 13-15 subjects (8.8%-11.0%) subjects with asthma.

6.1.10.1.3 Protocol VO34.04 Subject Disposition

**Figure 2. Disposition of subjects in Protocol VO34.04.**

From original BLA 125471/000; Clinical Study Report VO34.04, p.54



Source: Tables 14.1.1.1, 14.1.1.2 and 14.1.1.3  
AE = adverse event

6.1.11 Protocol VO34.04 Efficacy Analyses

**6.1.11.1 Protocol VO34.04 Analyses of Primary Endpoint(s)**

The primary efficacy endpoint for V034.04 was the average rhinoconjunctivitis total symptom score (ARTSS) during the grass pollen season. The ARTSS for each subject is calculated as the mean of all non-missing daily RTSSs during the pollen season, and ranges from 0 to 18. The data were analyzed by ANCOVA and the estimates for each group are reported as least square means (LS Mean). The point estimate, the difference in ARTSS LS Mean between placebo and each treatment group, and the 95% CI of these differences were extracted from the BLA.

**Table 9. Primary efficacy endpoint of Protocol VO34.04.**

Adapted from original BLA 125471/000; Clinical Study Report VO34.04, 65.

RTSS	Mean (SD)	Range	difference in adjusted means treatment – placebo; mean (95% CI)	Range
100 IR	4.72 (3.141)	0.0 – 13.4	-0.26 (-0.95; 0.43)	0.46
300 IR	3.58 (2.976)	0.0 – 15.1	-1.39 (-2.09; -.069)	0.0001
500 IR	3.74 (3.142)	0.0 – 14.2	-1.22 (-1.91; -.053)	0.0006
Placebo	4.93 (3.229)	0.0 – 14.2		

These data indicate that 300 IR and 500 IR were equally effective in decreasing the ARTSS, and that the 100 IR dose was not effective. Note that for each of these effective doses, the absolute value of the lower limit of the 95% CI is greater than 10% of the mean placebo point estimate symptom score (e.g. 0.53 > 10% of 4.93), indicating that a 10% improvement in the ARTSS is within the 95% CI.

Since subject withdrawals indicated that the 500 IR dose was not well tolerated, and since the 300IR and the 500IR doses appeared to be equally effective, the independent DSMB recommended that the 300 IR dose should be used for further clinical testing, and the sponsor agreed with the recommendation.

#### 6.1.11.2 Protocol VO34.04 Analyses of Secondary Endpoints

##### *Secondary Endpoint 1: Rescue medication usage*

There were no statistically significant differences between the active treatment groups versus Placebo Group with respect to rescue medication usage during the pollen period and during the worst part of the pollen period. These data are summarized in Table 11-7 in the Clinical Study Report.

##### *Secondary Endpoint 2: RSS for each of the six ARC symptoms*

The RSS for each symptom during the GPS was compared between placebo and each treatment group. The differences for each of these symptoms between the placebo group and the 300 IR group and the placebo group and the 500 IR group were significant ( $p < 0.03$ ). The data may be found in the table below was extracted from Table 11-8 in the CSR of Study VO34.04, Page 69.

#### 6.1.11.3 Protocol VO34.04 Subpopulation Analyses

No subpopulation analyses were critical for the review of safety and efficacy in this study.

#### 6.1.11.4 Protocol VO34.04 Dropouts and/or Discontinuations

Dropouts due to ‘lack of efficacy’ or an ‘AE’ were included in the PP analysis if they were otherwise valid. Where any of the six individual symptom scores for a given day was missing, the RTSS for that day was considered missing. Average RTSS scores were calculated using the non-missing data in the respective period. Missing data in the RQLQ were handled as per the questionnaire instruction manual. Incomplete dates were completed using the worst case scenario. No other imputation of missing values was performed.

#### 6.1.11.5 Protocol VO34.04 Exploratory and Post Hoc Analyses

##### *Combined Score*

For this analysis, the sponsors adjusted the RTSS upward depending on whether the subject used rescue medication. It is, therefore, rather than a “combined score,” an “adjusted score.” The specifics of the RTSS score adjustment are described on Pages 49-50 of the CSR. The point estimates, 95% CI, and p values for each treatment group versus placebo were extracted from Table 14.2.7.2, and are shown below.

**Table 10. Differences in Combined Score between each treatment group and the Placebo group**

Adapted from original BLA 125471/000; Clinical Study Report VO34.04, Tables 14.2.7.1 and 14.2.7.2

Treatment Group	Pt Estimate difference vs. Placebo	95% CI	p value
500 IR	-1.30	(-2.11; -0.50)	0.0015
300 IR	-1.76	(-2.58; -0.95)	<0.0001
100 IR	-0.25	(-1.06; 0.55)	0.5405

## 6.1.12 Safety Analyses

### 6.1.12.1 Protocol VO34.04 Methods

The first dose of the investigational product was taken in the presence of the investigator and the subject was observed for local and systemic reactions for 30 minutes. Throughout the rest of the study, the investigational product was self-administered at home by the subjects.

Subjects were issued an open ended diary card and kept a record of adverse events while out of the unit and reported to the clinical staff at the following visit.

### 6.1.12.2 Protocol VO34.04 Overview of Adverse Events

Each of the treatment groups had a higher number of Treatment Emergent Adverse Events (TEAE) than placebo (48.7%). For the treatment groups, the incidence was 64.4%, 62.6%, and 68.8%, for the 100 IR, 300 IR, and 500 IR groups respectively.

As anticipated by what is currently known about allergy immunotherapy, previous experience with SLIT, and Protocol VO34.04DK, TEAE were most commonly categorized in the SOC “Gastrointestinal disorders” (~40% per treatment group and most commonly were oral pruritus and paresthesia) and “Respiratory, thoracic, and mediastinal disorders” (~25% in each treatment group; throat irritation). There were also a high percentage of AE in the “Infections and Infestations” category, none of which are considered related to treatment, and was not increased above placebo in any of the study drug groups.

### 6.1.12.3 Protocol VO34.04 Deaths

There were no deaths in this study.

### 6.1.12.4 Protocol VO34.04 Nonfatal Serious Adverse Events

There were three non-fatal SAE in the study, one episode of back pain, one subject with abdominal pain and suspicion for appendicitis, and one subject with severe intervertebral disc protrusion. These were considered by the sponsor as not related to the study drug. The reviewer concurs with this assessment.

### 6.1.12.5 Protocol VO34.04 Adverse Events of Special Interest (AESI)

In the context of the allergenic activity of the product, anticipated AESI are systemic anaphylaxis and laryngopharyngeal swelling that may obstruct airflow. Neither of these occurred in this study.

### 6.1.12.6 Protocol VO34.04 Clinical Test Results

There were no abnormalities in the mean values of clinical test results.

### 6.1.12.7 Protocol VO34.04 Dropouts and/or Discontinuations

Withdrawals were most highly represented in the 500 IR treatment group (8 subjects, 5.0%). From the 300 IR dose group, 6 subjects (3.9%) withdrew, and from the 100 IR dose group, 3 subjects (1.9%) withdrew. The product-related AE that lead to dropouts are included among those that are expected with either allergen immunotherapy or

specifically with SLIT; the percentage of subjects who did not tolerate SLIT is lower than the percentage of subjects who are unable to tolerate SCIT. Note that while the intensity of the AE were either moderate or severe, there were no SAE that precipitated withdrawal from the study.

**Table 11. Subject withdrawals in Protocol VO34.04**

Adapted from original BLA 125471/000; Clinical Study Report VO34.04, Table 12-3, p.87

Treatment Group	Subject #	Preferred Term	Outcome	Intensity	Relationship	Serious
100 IR	01373	Oral Pain	Resolved	Severe	Certain	No
100 IR	19113	Urticaria Localised	Resolved	Moderate	Possible	No
100 IR	40103	Oesophagitis	Resolved	Severe	Possible	No
300 IR	08435	Oropharyngeal Swelling	Resolved	Moderate	Certain	No
300 IR	15555	Pregnancy	-	Severe	Not Related	No
300 IR	18034	Rhinitis	Resolved	Severe	Certain	No
300 IR	18080	Abdominal Pain Upper	Resolved	Moderate	Probable/Likely	No
300 IR	26129	Oral Pruritus	Resolved	Moderate	Certain	No
300 IR	38325	Abdominal Pain Upper	Resolved	Moderate	Possible	No
500 IR	01333	Dysphagia	Resolved	Severe	Certain	No
500 IR	01371	Oral Pain	Resolved	Severe	Certain	No
500 IR	08246	Dermatitis Atopic	Resolved with Sequelae	Moderate	Certain	No
500 IR	16058	Oropharyngeal Swelling	Resolved	Moderate	Possible	No
500 IR	19203	Cough	Resolved	Moderate	Probable/Likely	No
500 IR	26408	Oral Pruritus	Resolved	Severe	Certain	No
500 IR	41036	Rhinitis	Resolved	Severe	Certain	No
500 IR	46441	Oral Pruritus	Resolved	Severe	Certain	No

#### 6.1.13 Reviewer Summary of Protocol VO34.04

Study VO34.04 was a Phase 2 study of adults 18-45 years of age that met its primary endpoint because 300 or 500 IR of the study drug administered daily 4 months prior to and during GPS improved the RTSS compared to placebo. As a secondary endpoint, the CS, the parameter that CBER accepts for proof of efficacy, was also improved in the 300 or 500 IR study drug group. There was no difference in clinical scores between the 100 IR study drug and placebo groups, and no apparent difference in efficacy between the 300 and 500 IR doses.

There were no SAE, but moderate to severe AE precipitated withdrawal among a higher percentage of subjects in the study drug groups. Because the incidence of AE was higher in the 500 IR group than the 300 IR group, the 300 IR dose was chosen for further study.

#### **6.2 Trial #2 (supportive for inclusion of pediatric subjects in the indications for use)**

*Protocol VO52.06: A randomized, DBPCR, multi-national, multicenter, Phase 3 pediatric study of the efficacy and safety of 300 IR SLIT administered as allergen-based tablets once daily to children suffering from grass pollen rhinoconjunctivitis.*

### 6.2.1 Protocol VO52.06 Objectives

Primary Objective: To assess the efficacy of SLIT for grass pollen allergens on the Rhinoconjunctivitis Total Symptom Score (RTSS) of the six rhinoconjunctivitis symptoms (namely sneezing, rhinorrhea, nasal pruritus, nasal congestion, ocular pruritus, and watery eyes).

Secondary Objectives: To assess the efficacy of SLIT for grass pollen allergens on the:

- Rescue medication score (RMS) and usage (use of antihistamine [oral form and/or eye drops], nasal corticosteroid and oral corticosteroid).
- Combined Score (CS) - a score taking into account the RTSS and RMS.
- Each of the six individual Rhinoconjunctivitis Symptom Scores (RSS).
- Proportion of symptom-free days.
- Global evaluation of the efficacy of SLIT for grass pollen allergens by the subject.
- To document the safety of the treatment.

### 6.2.2 Protocol VO52.06 Design Overview

Protocol VO52.06 was a randomized, double-blind, placebo-controlled trial of safety and efficacy of ORALAIR, 300 IR, in children and adolescents.

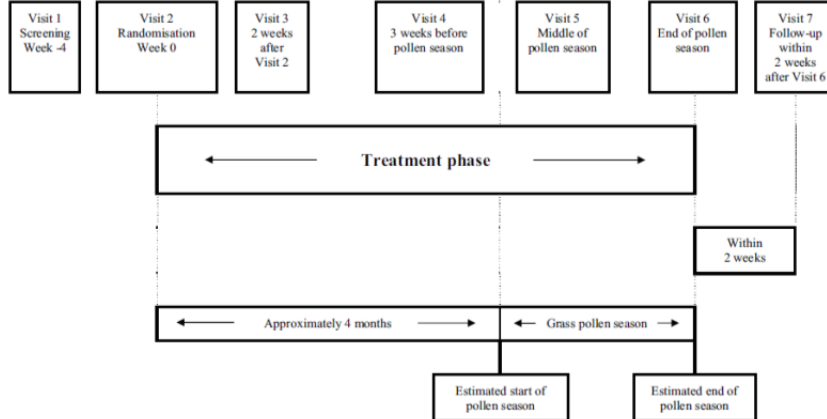
Phase:	Phase 3
Subject Population:	Children, ages 5-17 inclusive with AR
Randomization/Blinding:	RDBPC
Location of Study:	Denmark, France, Germany, Poland, Spain
Number of Study Centers:	29 Centers
Study Period:	16 Dec 2006 through 12 Sept 2007

#### Protocol VO52.06 Duration of Study:

Total Study:	Approximately 10 months
Screening:	One month maximum
Treatment:	Eight months
Follow-up:	Approximately one month
Number of Visits:	7

### Figure 3. Study Design of VO52.06

From original BLA 125471/000; Clinical Study Report VO52.06, p. 26



#### 6.2.3 Population of Protocol VO52.06

##### Protocol VO52.06 Subject Criteria (relevant to allergic diseases and asthma)

###### Inclusion:

Children 5-17 years of age  
ARC for at least two pollen seasons prior to the study  
+SPT (geometric wheal diameter > 3 mm) to the 5 grass pollen allergen extract  
Specific IgE positive to grass pollen (>Class 2)  
RRTSS score  $\geq 12$   
If asthmatic, FEV1 > 80% of normal

###### Exclusion:

Sensitization to pollens (other than the five grass pollens in ORALAIR) which are airborne during grass pollen season  
ARC due to perennial allergens  
Asthma that requires daily treatment or medications other than beta-2 agonists

#### 6.2.4 Protocol VO52.06 Study Treatments or Agents Mandated by the Protocol

Subjects received tablets of either placebo or grass pollen SLIT at a dose of 100 IR the first day (one tablet), 200 IR the second day (two tablets), and 300 IR (one tablet) thereafter starting at Visit 2. Dosing was escalated as shown below. On Day 2, the placebo group received two tablets of placebo as expected for a blinded study. The first dose was taken in the presence of the Investigator, and subjects were observed for local and systemic reactions for 30 minutes after administration of the investigational products.

For the study product, lyophilised extracts of the relevant allergens extracts of five grasses (cocksfoot [*Dactylis glomerata*], meadow grass [*Poa pratensis*], rye grass [*Lolium perenne*], sweet vernal grass [*Anthoxanthum odoratum*], timothy grass [*Phleum pratense*]) were reconstituted with a diluent in order to obtain a 'parent compound' with an immunologic activity equal to 100 IR/mL. The in-house reference extract labeled 100 IR is defined as the concentration eliciting by SPT a geometric mean wheal size of 7 mm diameter when tested in 30 subject sensitive to the corresponding allergen. Formulation,

batch numbers and manufacture and expiry dates of the investigational product are shown in the table below. Stallergenes manufactured both the study drug and placebo tablets.

**Table 12. Study Drug and Placebo used for Protocol VO52.06**

Adapted from BLA 125471/000; Clinical Study Report VO52.06, p.32

	<b>Study Drug</b>	<b>Placebo</b>
Formulation	Tablets containing freeze-dried allergen extracts of five grasses, supplied in strengths of 100 IR, 300 IR, cellulose (microcrystalline), croscarmellose sodium, silica (colloidal anhydrous), magnesium stearate, lactose monohydrate	Tablets matching the active treatment in size, shape and colour and containing caramel, quinolene yellow, cellulose (microcrystalline), croscarmellose sodium, silica (colloidal anhydrous), magnesium stearate, lactose monohydrate
Batch numbers	100 IR: P0122, 300 IR: P0123	P0131
Date of manufacture	27 April 2006	05 July 2006
Expiry Date	September 2007	September 2007

#### 6.2.5 Protocol VO52.06 Directions for Use

Subjects were instructed to leave the tablet(s) under the tongue until complete dissolution before swallowing. From Day 3 of treatment (after ramping up the dose) the subjects took one tablet of 300 IR of study drug or placebo sublingually, daily, until Visit 6.

#### 6.2.6 Protocol VO52.06 Sites and Centers

This study was conducted by 29 Investigators at 29 study centers in five European countries (Denmark, France, Germany, Poland and Spain).

#### 6.2.7 Protocol VO52.06 Surveillance/Monitoring

The safety of the investigational product was evaluated by monitoring AE through the use of daily diary cards (passive) and history/physical examinations (active) during the study visits. The CRF forms for active surveillance were included in the IND and BLA submissions, and were appropriate.

#### 6.2.8 Protocol VO52.06 Endpoints and Criteria for Study Success

Primary Endpoint: Efficacy defined by a mean decrease of 20% of the ARTSS

Critical Secondary Endpoints:

Rescue medication usage (Average RMS)

Average CS

Average RSS



### 6.2.9 Protocol VO52.06 Statistical Considerations & Statistical Analysis Plan

The study tested the hypothesis that the RTSS over the grass pollen season is no different in the treatment groups compared to the placebo group of children and adolescents. The power analysis and treatment of missing data points were adapted from the CSR.

#### Power analysis of study

(Adapted from sBLA 125471/000; Clinical Study Report VO52.06, p.45)

Given an alpha = 0.05 and a common standard deviation = 3.261 (SD of 3.106 inflated with 5%), the results of Study VO34.04 suggested that a sample size of 117 subjects per treatment group will have a power of 80% to detect a mean difference of 1.2, that is, an average difference of 0.20 per symptom (1.2/6) between Placebo and 300 IR in the average RTSS during the pollen period while on treatment. Assuming a 20% screening failure rate and a 15% drop-out rate it was decided to screen 350 subjects in order to have 140 randomized subjects in each treatment group at the start of the study.

#### Treatment of missing data points

(Adapted from sBLA 125471/000; Clinical Study Report VO52.06, p.72)

When any of the six individual symptom scores for a given day was missing, the RTSS for that day was considered missing. Average RTSS scores were calculated using the non-missing data in the respective period for the primary efficacy variable. An additional supportive analysis was performed using all randomized subjects, imputing missing average RTSS using Proc MI in SAS if the subject was excluded from the ITT population for not having an average RTSS. The proportion of valid RTSS days during the pollen period was summarized by treatment group for the ITT and PP populations to evaluate the extent of missing RTSS data. Subjects with missing average RTSS were listed together with the reason for the missing average RTSS. Incomplete dates were completed using the worst case scenario where applicable.

Please refer to the Statistical Review for more information.

### 6.2.10 Study Population and Disposition

#### 6.2.10.1 Populations Enrolled/Analyzed

##### Protocol VO52.06 Number of Subjects:

Planned (enrolled/randomized):	280
Screened:	320
Randomized:	278
Safety population:	278
ITT population:	266
PP population:	227

The safety population included all subjects who received at least one dose of the investigational product.

The Intention to Treat (ITT) population was considered primary for the efficacy analysis and included all subjects who received at least one dose of the investigational product and had an RRTSS and at least one RTSS during the pollen period while on treatment.

The PP population included all subjects who completed the study according to the protocol and had no major protocol violations. Subjects had to qualify for inclusion in the ITT population in order to be included in the PP population. Subjects who were withdrawn from the study due to lack of efficacy or an AE related to the investigational product were included in the PP population if they were otherwise valid.

#### *6.2.10.1.1 Demographics*

There were no significant differences between the study drug and placebo groups in the safety, ITT, or PP group among the following variables: gender, age group (5-11 and 12-17 years), age, weight, height, or BMI.

#### *6.2.10.1.2 Medical/Behavioral Characterization of the Enrolled Population*

The distribution among subjects in each dose group for use of drugs unrelated to ARC was equivalent between treatment groups. Drugs in the ATC Class “Respiratory System” were the most common concomitant medications. These included topical and systemic antihistamines, topical decongestants, all of which are used to treat ARC. Inhalant adrenergics were used equally among the treatment groups, which is consistent with equivalent prevalence of asthma in each treatment group (20.1% and 19.4%, respectively).

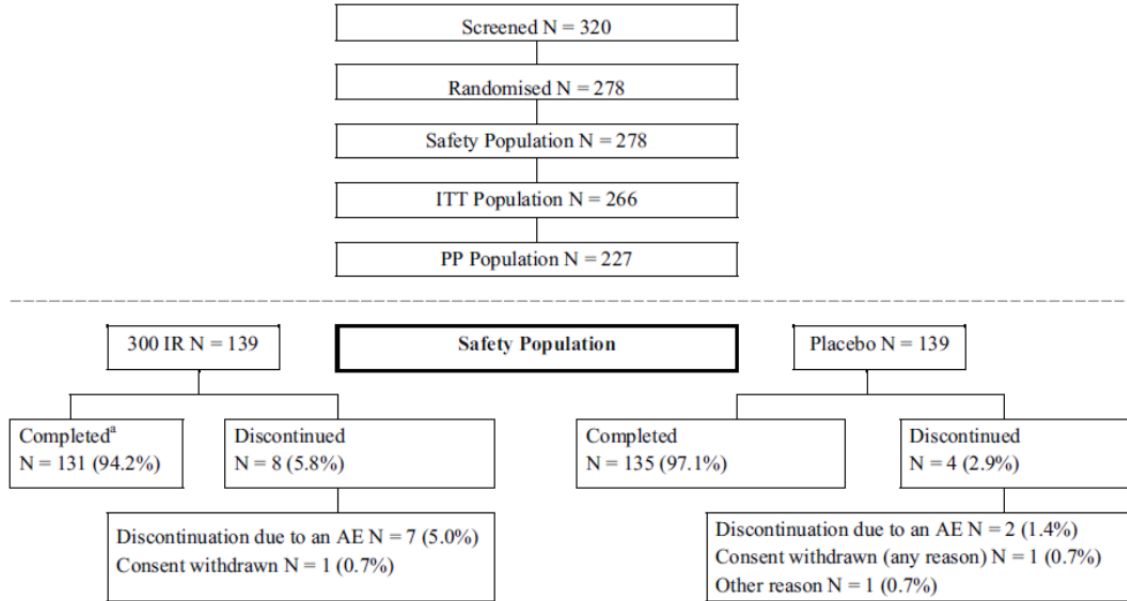
Each study group included 13-15 subjects (8.8%-11.0%) subjects with asthma. Only asthmatic subjects with FEV1 > 80% of normal and who are not taking daily medication for asthma were randomized.

An additional major variable is whether the subjects were sensitized only to grass pollen, or to additional allergens. Since the subjects were skin-tested with a 5-mix grass pollen extract, there was no distinction between sensitivity to one versus two or more grass pollens—all were considered “mono-allergic.” Subjects who were also allergic to weeds, trees, and other environmental allergens were considered “poly-allergic.” The percentages of mono- and poly- allergic subjects in each treatment group were similar (40.7% Placebo versus 41.2% Study Drug).

6.2.10.1.3 Protocol VO52.06 Subject Disposition

**Figure 4. Disposition of subjects in Protocol VO52.06.**

from sBLA 125471/000; Clinical Study Report VO52.06, p.54



N = Number of patients; % = Percentage of patients; AE: Adverse event; IR: Index of reactivity; ITT: Intention to Treat; PP: Per Protocol.  
<sup>a</sup> End of study CRF pages were missing for 3 (2.2%) patients (Patient 0418/26, Patient 0418/28 and Patient 0421/03) in 300 IR. However, these patients did complete the study.  
Source: Section 14, Table 14.1.1.1 (page 99), Table 14.1.1.2 (page 100) and Table 14.1.1.3 (page 101).

6.2.11 Protocol VO52.06 Efficacy Analyses

**6.2.11.1 Protocol VO52.06 Analyses of Primary Endpoint(s)**

Study VO52.06 Efficacy Results:

Protocol VO52.06 of efficacy and safety in children was appropriately designed to meet its endpoint of a decrease in the ARTSS in the study drug group compared to placebo. The study met its primary endpoint in both the ITT and PP populations. As shown in the table extracted from the sponsor’s BLA application, the study met its primary endpoint. The ARTSS in the ITT population was decreased by a point estimate of 28.0% (3.31/4.45), with 95% CI (-2.00, -0.49; -10.9%, -44.3%) over the entire GPS, with a comparable decrease over the “worst pollen period” (defined as the most intensive pollen period over approximately 10 to 14 days per study center).

**Table 13. RTSS among study drug and placebo groups in Protocol VO52.06**

from BLA 125471/000; Clinical Study Report VO52.06, p.67

Period	Treatment (N)	Mean	SD	Minimum	Median	Maximum
Entire pollen season	300 IR (131)	3.25	2.86	0	2.48	18.00
	Placebo (135)	4.51	2.93	0	4.08	14.65
Worst pollen period	300 IR (129)	3.69	3.14	0	2.88	18.00
	Placebo (133)	5.11	3.39	0	5.04	17.60

**Table 14. Improvement of RTSS by study drug in ITT versus PP populations**

from BLA 125471/000; Clinical Study Report VO52.06, p.66

Period	Treatment (N)	Mean improvement	Median Improvement
Entire pollen season	ITT	-28.0%	-39.3%
	PP	-25.9%	-37.6%
Worst pollen period	300 IR (129)	-27.9%	-42.9%
	Placebo (133)	-24.0%	-40.0%

Statistical analysis of these differences gave the following results:

**Table 15. Analysis by ANCOVA of RTSS of study drug and placebo groups**

from BLA 125471/000; Clinical Study Report VO52.06, p.65

Source	Point Estimate	95% CI	P-value
ANCOVA	-1.13	-1.80, -0.46	0.0010
Non-parametric	-1.28	-1.91, -0.65	<0.0001

#### 6.2.11.2 Protocol VO52.06 Analyses of Secondary Endpoints

Secondary Endpoint 1: Decrease in Rescue Medication Score (RMS):

The use of rescue medication by the ITT population of the treatment group was decreased compared to placebo (0.53/0.73). This difference of -0.20 translates to a point estimate decrease of 27.0%, with 95% CI of -8.2% to -46.5%. The p values for the ANCOVA and non-parametric analyses were 0.006 and 0.019, respectively (from sBLA 125471/000; Clinical Study Report VO52.06, p.70)

Secondary Endpoint #2: Decrease in Average Combined Score (ACS):

The CS of the ITT population of the treatment group was decreased compared to placebo (0.57/0.77), with a difference of -0.20 which translates to a point estimate decrease of 26.0%, with 95% CI of -11.7% to -39.0%. The p values for the ANCOVA and non-parametric analyses were each 0.0004 (from sBLA 125471/000; Clinical Study Report VO52.06, p.70)

#### 6.2.11.3 Subpopulation Analyses

There are no special populations in this study group.

#### 6.2.11.4 Dropouts and/or Discontinuations

Subjects who discontinued their participation in the study due to 'lack of efficacy' or an 'AE' were included in the PP analysis if they were otherwise valid. The tabular listing of subject withdrawals due to AE is found in Section 6.2.12.6.

#### 6.2.11.5 Exploratory and Post Hoc Analyses

##### Immunological Markers

The geometric mean IgG4 ( $\mu\text{g/L}$ ) more than tripled from Visit 1 to Endpoint for 300 IR (Ratio: 3.37), while for Placebo rose slightly (Ratio: 1.41). The geometric mean IgE (kU/L) was similar at Visit 1 and Endpoint for 300 IR (Ratio: 1.35), but slightly higher for Placebo at Endpoint compared to Visit 1 (Ratio: 1.64).

### Skin Prick Test

Eight and six subjects in the 300 IR study drug and Placebo groups, respectively, had a negative SPT at Endpoint. Subjects in the 300 IR study drug group had a larger mean decrease in mean wheal diameter from Visit 1 to Endpoint than subjects in the Placebo group (-1.73 mm and -0.77 mm, respectively).

### Asthma Evaluation

Of the 22 subjects in 300 IR and 24 subjects in Placebo who were considered to have asthma at Visit 1, 6 subjects in 300 IR and 12 subjects in Placebo no longer had symptoms of asthma at Endpoint.

Of the 109 subjects in 300 IR study drug and 111 subjects in the Placebo group who were considered not to have asthma symptoms at Visit 1, eight and nine subjects in the 300 IR in the Placebo group had symptoms of asthma at Endpoint. These trends did not suggest benefit or harm to subjects with asthma.

## 6.2.12 Safety Analyses

### **6.2.12.1 Methods**

The safety of the investigational product was evaluated by monitoring the subject's AE profile from daily open-ended diary cards, physical examination findings (including vital signs) and by the assessment of routine clinical laboratory safety tests (performed at screening and end of treatment).

### **6.2.12.2 Overview of Adverse Events**

As expected, the incidence of respiratory disorders in each study group was similar. There were more drug-related AE in the treatment group, and more AE that led to study withdrawal in the treatment group. There were no SAE or deaths. Most of the TEAE in the subjects in the treatment group that were considered related to the study drug were consistent with application site reactions (e.g. tongue, lips, and classified as Gastrointestinal Disorders) and were Grade 1 or 2 (according to the WAO classification: mild or moderate severity that did not require discontinuation of therapy. The incidence of headaches was also increased in the study drug group.

Of interest, the incidence of "wheezing" was greater in the placebo group (9.4% placebo group, 5.8% study drug group) while reports of "asthma" were greater in the study drug group (4.3% placebo group, 7.2% study drug group). Taken together, it is difficult to infer that there was any impact of the study drug on subset of children with asthma, particularly in the context of the low number of study subjects. Severe (non-serious) TEAE reported by greater than 5% of subjects in the Safety Set are shown in Table 18.

**Table 16. Severe (non-serious) AE in Protocol VO52.06**

Adapted from the original submission, BLA 125471/000, CSR VO52.06, Table 23, Page 80.

	<b>Adverse Event</b>	<b>Study Drug #subjects [percent]</b>	<b>Placebo #subjects [percent]</b>
Respiratory mediastinal and thoracic	Cough	2 [1.4]	2 [1.4]
Respiratory mediastinal and thoracic	Throat irritation	1 [0.7]	0
Respiratory mediastinal and thoracic	Nasal congestion	2 [1.4]	0
Respiratory mediastinal and thoracic	Rhinorrhea	1 [0.7]	1 [0.7]
Respiratory mediastinal and thoracic	Wheezing	1 [0.7]	0
Respiratory mediastinal and thoracic	Pharyngolaryngeal pain	2 [1.4%]	0
Respiratory mediastinal and thoracic	Throat tightness	1 [0.7]	0
Respiratory mediastinal and thoracic	Epistaxis	0	1 [0.7]
Gastro-intestinal Disorders	Oral pruritus	4 [2.9]	0
Gastro-intestinal Disorders	Mouth edema	1 [0.7]	0
Gastro-intestinal Disorders	Abdominal pain	1 [0.7]	0
Gastro-intestinal Disorders	Mucosal blistering	1 [0.7]	0
Gastro-intestinal Disorders	Oral discomfort	1 [0.7]	0
Infections	Nasopharyngitis	1 [0.7]	8 [5.8]
Infections	Tonsillitis	1 [0.7]	8 [5.8]
Infections	Inf. Mononucleosis	1 [0.7]	8 [5.8]
Infections	Viral infection	1 [0.7]	8 [5.8]
Infections	Eye infection	0	1 [0.7]
Skin Disorders	Atopic Dermatitis	1 [0.7]	
Skin Disorders	Rash	1 [0.7]	
Skin Disorders	Pruritus		1 [0.7]
Eye Disorders	Conjunctivitis	1 [0.7]	0
Eye Disorders	Eye pruritus	0	1 [0.7]
Nervous System	Headache	1 [0.7]	1 [0.7]
Nervous System	Syncope	1 [0.7]	0
Ear	Ear discomfort	1 [0.7]	0
Other	Chest discomfort	2 [1.4%]	0
Other	Fatigue	1 [0.7]	0
Other	Chest Pain	1 [0.7]	0

### 6.2.12.3 Deaths

There were no deaths in the study.

### 6.2.12.4 Nonfatal Serious Adverse Events

One subject each in the treatment group had a synovial cyst and Burkett's lymphoma, and one placebo subject had a muscle strain, and one placebo subject presented with inadequately controlled Diabetes Mellitus. None of these were considered related to the study drug by the investigators.

*The reviewer concurs with "not related to study drug" assessment of these AE*

### 6.2.12.5 Adverse Events of Special Interest (AESI)

Subject 0103/04 in the 300 IR study drug group presented with mild exacerbation of asthma 124 days after first administration of the investigational product. The event was considered not related to the administration of investigational product. In the opinion of

the investigator this event was related to the subject's pre-existing medical condition and was probably triggered by high levels of grass pollen; no action was taken and the event resolved after 2 days.

*The reviewer concurs with "not related to study drug" assessment of the AE*

Subject 0103/18 in the 300 IR group was hospitalized for further investigation and severe Burkitt's lymphoma was diagnosed 61 days after first administration of the investigational product. The event was considered not related to the administration of the investigational product; the subject was hospitalized and the event was ongoing at the end of the study. The outcome of the event is unknown.

*The reviewer concurs with "not related to study drug" assessment of the AE*

Subject 0209/09 in Placebo group presented with severe abdominal pain 8 days after first administration of the investigational product that was apparently appendicitis. The event was considered unlikely related to the administration of the investigational product, but the administration (of placebo) was discontinued.

*The reviewer concurs with "not related to study drug" assessment of the AE*

Subject 0417/15 in Placebo group presented with moderate polytraumatism 12 days before the first dose of the investigational product. The event was considered not related to the administration of the investigational product; the subject was hospitalized and the event resolved after 5 days.

*The reviewer concurs with "not related to study drug" assessment of the AE*

Subject 0421/19 in Placebo group presented with moderate gastroduodenitis 80 days after first administration of the investigational product. Even though the event was considered not related to the investigational product, administration was temporarily discontinued. The subject was hospitalized and the event resolved after 13 days.

*The reviewer concurs with "not related to study drug" assessment of the AE*

#### **6.2.12.6 Clinical Test Results**

There were no significant abnormalities in the clinical laboratory tests or vital signs.

#### **6.2.12.7 Dropouts and/or Discontinuations**

Shown below are the subjects in the Safety Set who withdrew from the study due to an AE. The reviewer concurs with the assessed relationship of the AE to study drug (in those in the 300 IR treatment group). These AE are consistent with those that are anticipated with this product and do not impact on the overall evaluation of safety of the product.

**Table 17. Subject withdrawals from Protocol VO52.06**

from BLA 125471/000; Clinical Study Report VO52.06, p.87

Treatment Group	Patient number	Preferred Term <sup>a</sup>	Outcome	Intensity	Relationship	Serious
300 IR	0101/02	Chest discomfort	Resolved	Severe	Certain	No
300 IR	0101/12	Oral mucosal blistering	Resolved	Moderate	Probably/likely	No
300 IR	0101/13	Oral pruritus	Resolved	Severe	Certain	No
300 IR	0103/18	Oral pruritus	Resolved	Severe	Probably/likely	No
300 IR	0416/03	Oral pruritus	Resolved	Mild	Possible	No
300 IR	0417/12	Oedema mouth	Resolved	Mild	Certain	No
300 IR	0528/06	Vomiting	Resolved	Moderate	Unlikely	No
Placebo	0103/02	Diabetes Mellitus inadequate control	Resolved	Severe	Probably/likely	No
Placebo	0209/09	Abdominal pain	Resolved With sequelae <sup>b</sup>	Severe	Unlikely	Yes

IR: Index of Reactivity; MedDRA: Medical Dictionary for Regulatory Activities.

<sup>a</sup> Adverse events were coded using MedDRA Version 9.1.

<sup>b</sup> Appendectomy scar.

Source: Section 14, Table 14.3.2.1 (page 344) and Listing 16.2.7.3 (Appendix 16.2).

#### 6.2.13 Study VO52.06 Reviewer's conclusions:

Study VO52.06 tested for safety and efficacy in subjects ages 5-17 with mild to moderate ARC. In this small cohort of children who are healthy other than ARC with or without mild asthma, there were no SAE associated with ORALAIR. There were AE that were serious in intensity, but there were no TEAE SAE, deaths or hospitalizations. Protocol VO52.06 met its primary efficacy endpoint with > 20% decrease in the use of rescue medication and combined medication and symptom scores (ARMS and ACS, respectively).

### 6.3 Trial #3 (Supportive for safety and efficacy)

*Protocol VO53.06: A randomized, double-blind, placebo-controlled, multinational, multi-center, Phase III study to assess the long term efficacy, carry-over effect and safety of two dosing regimens of 300 IR sublingual immunotherapy (SLIT) administered as allergen-based tablets once daily to subjects suffering from grass pollen rhinoconjunctivitis.*

#### Protocol VO53.06 Study Synopsis

Protocol VO53.06 was a multiyear European Phase 3 trial to determine whether treatment with ORALAIR over three successive years maintains or enhances efficacy, and whether efficacy is maintained over the subsequent two years after treatment has ceased. The parameter used to assess efficacy is the Average Adjusted Symptom Score (AASS), which is a score that combines the total symptom score (RTSS) and the daily rescue medication use according to an algorithm described in Reference 10.

Study subjects with ARC were randomized to two treatment groups and one placebo group. While each treatment group took ORALAIR 300 IR sublingually every day during the pollen season, one group began taking ORALAIR 4 months prior to the onset of grass



pollen season, and the other began taking the ORALAIR 2 months prior to the onset of grass pollen season. Each group followed its regimen for three years, after which the subjects were observed for two years.

### 6.3.1 Protocol VO53.06 Objectives (Primary, Secondary, etc)

**Primary Objective:** To assess the clinical effect of two dosing regimens of 300 IR sublingual tablets of grass pollen allergen extract compared to placebo on allergic rhinoconjunctivitis symptoms and symptomatic medication use, over the third pollen season using the Average Adjusted Symptom Score (AASS), and for long-term efficacy, during the two years of post-treatment observation.

#### Secondary Objectives (relevant to decision to approve the BLA):

To assess the efficacy over the first pollen season, the sustained clinical efficacy on treatment over the second and the third pollen seasons and post-treatment long-term efficacy of 300 IR SLIT for grass pollen allergens on:

- The Average Rhinoconjunctivitis Total Symptom Score (ARTSS) of the six rhinoconjunctivitis symptoms sneezing, rhinorrhea, nasal pruritus, nasal congestion, ocular pruritus and watery eyes.
- The Average Rescue Medication Score (ARMS) and use of rescue medication (antihistamine [oral form or/and eye drops], nasal corticosteroid and oral corticosteroid).
- Each of the six individual Average Rhinoconjunctivitis Symptom Scores (ARSS).
- The Average Combined Score (ACS): a score taking into account the RTSS and Rescue Medication Score (RMS).

### 6.3.2 Protocol VO53.06 Design Overview

#### Protocol VO53.06 Study Design

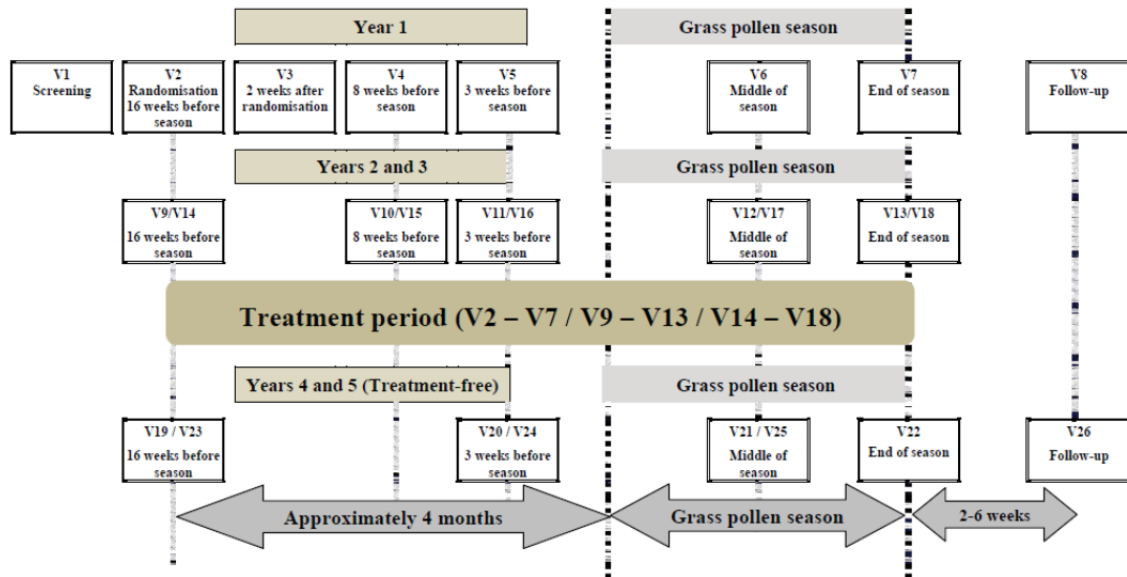
Phase: Phase 3, RDBPC  
Subject Population: Adults ages 18 to 50 years (inclusive)  
Randomization/Blinding: RDBPC  
Location of Study: Austria, Canada, Czech Republic, Denmark, France, Germany, Italy, Poland, Russia and Slovakia  
Number of Study Centers: Year 1: 48; Year 2: 47; Years 3, 4 and 5: 45

#### Protocol VO53.06 Duration of Study:

Total Study: 26December2006 to 7September2011  
Screening: Approximately 4 weeks  
Treatment: Approximately 4 or 6 months per year for three years  
Follow-up: Two years  
Number of Visits: Year 1: 8; Years 2 and 3: 5 each; Years 4 and 5: 5 each

**Figure 5. Design of Protocol VO53.06**

from BLA 125471/000; Clinical Study Report VO53.06 Years 1 to 4, p.32



Protocol VO53.06 was well designed to demonstrate that administration of ORALAIR for two consecutive years is safe and effective for the treatment of ARC due to grass pollen allergy (one or a combination of the five pollens included in the extract). The study also demonstrated that the effect of immunotherapy with ORALAIR is sustained for an additional year after discontinuation, but that the benefits are not sustained in the second year after therapy.

6.3.3 Population

Protocol VO53.06 Subject Criteria (relevant to ARC)

Inclusion: Adults, 18-50 years of age  
Seasonal grass pollen-related ARC  $\geq 2$  pollen seasons  
+SPT (geometric wheal diameter  $> 3$  mm) to the 5 grass pollen allergen extract  
Specific IgE positive to grass pollen ( $>$ Class 2)  
RRTSS score  $\geq 12$

Exclusion: Sensitization to pollens (other than the five grass pollens in ORALAIR) which are airborne during grass pollen season  
ARC due to perennial allergens  
Asthma that requires treatment other than beta-2 inhaled agonists.

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

##### **Table 18. Investigational agents used in Protocol VO53.06**

from BLA 125471/000; Clinical Study Report VO53.06 Years 1 to 4, p.38

The formulation is identical to that described in 6.2.4 for Study VO52.06. The manufacturer of study drug and placebo is Stallergènes.

	<b>Investigational Drug</b>	<b>Placebo</b>
<b>Batch numbers</b>	Year 1: P0123 and P0133 Year 2: 302 Year 3: P0239	Year 1: P0132 Year 2: P0188 Year 3: P0236
<b>Manufacturer</b>	Stallergènes S.A.	Stallergènes S.A.
<b>Date of manufacture</b>	Year 1: 27 April 2006 and 01 June 2006 Year 2: March 2007 Year 3: May 2008	Year 1: 05 June 2006 Year 2: May 2007 Year 3: May 2008
<b>Expiry date</b>	Year 1: September 2007 and November 2007, respectively Year 2: March 2009 Year 3: April 2010	Year 1: November 2007 Year 2: May 2009 Year 3: April 2010

#### 6.3.5 Directions for Use

One tablet, under the tongue until complete dissolution before swallowing

#### 6.3.6 Protocol VO53.06 Sites and Centers

The Principal Coordinator of the study was Professor Alain Didier in Toulouse, France. There were between 45-48 study centers in eight EU countries (Austria, Czech Republic, Denmark, France, Germany, Italy, Poland, Russia and Slovakia) and Canada.

The Contract Research Organization (CRO) that managed this study was (b)(4). (b)(4) wrote the protocol, developed the CRF, and managed the data, including statistical analysis. Writing, CRF development, data management, statistical analysis were done by (b)(4) on behalf of Stallergènes S.A. (b)(4) and local affiliates in each participating country performed study and medical monitoring. Pharmacovigilance, quality assurance and regulatory activities were managed by (b)(4).

#### 6.3.7 Protocol VO53.06 Surveillance/Monitoring

The safety of the investigational product was evaluated by monitoring AE through the use of daily diary cards (passive) and history/physical examinations (active) during the study visits. A DSMB monitored the study and made the decision to continue with the study after the first year. The CRF forms for active surveillance were included in the IND and BLA submissions, and were appropriate.

##### **Table 19. Visit Schedule and surveillance monitoring of Protocol VO53.06**

From original BLA 125471/000; Clinical Study Report VO53.06 Years 1 to 5, p. 35

Study Assessment	Year 1 First pollen season V1	Year 1 First pollen season V2	Year 1 First pollen season V3	Year 1 First pollen season V4	Year 1 First pollen season V5	Year 1 First pollen season V6	Year 1 First pollen season V7	Year 1 First pollen season V8	Year 2 and 3 Second and third pollen seasons V9	Year 2 and 3 Second and third pollen seasons V10	Year 2 and 3 Second and third pollen seasons V11	Year 2 and 3 Second and third pollen seasons V12	Year 2 and 3 Second and third pollen seasons V13	Year 4 and 5 Fourth and fifth pollen seasons V19	Year 4 and 5 Fourth and fifth pollen seasons V20	Year 4 and 5 Fourth and fifth pollen seasons V21	Year 4 and 5 Fourth and fifth pollen seasons V22	Year 4 and 5 Fourth and fifth pollen seasons V23	Year 4 and 5 Fourth and fifth pollen seasons V24	Year 4 and 5 Fourth and fifth pollen seasons V25	Year 4 and 5 Fourth and fifth pollen seasons V26
Written consent	X													X							X
Medical and allergy history	X																				
Demographics	X								X					X							
Asthma evaluation	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination (including vital signs)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Retrospective Rhinoconjunctivitis Total Symptom Score	X																				
Pregnancy test (urine)	X	X							X				X	X							X
Safety laboratory tests	X																				X
Immunological markers	X																				X
Skin prick test	X																				X
Eligibility of patient	X								X												X
Randomisation	X																				
Economic evaluation						X						X									X
Global evaluation of the efficacy of the investigational products							X														X
Rhinoconjunctivitis Quality of Life Questionnaire						X															X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Investigational products dispense / check/ return																					
Daily record card dispense / check /return				X	X	X	X	X				X	X							X	X
Rescue medication dispense / check / return					X	X	X	X				X	X							X	X

### 6.3.8 Protocol VO53.06 Endpoints and Criteria for Study Success

Primary Endpoint: Efficacy was based on the AASS, a score that takes into account the RTSS and RMS use (study drug versus placebo) during the grass pollen season\*. The primary endpoint was met if the AASS of the study drug group was decreased by at least 20% of the placebo group (i.e. AASS of study drug group  $\leq$  80% of AASS of placebo group).

The pollen period was defined as the first day out of three consecutive days with a grass pollen count of 30 grass pollen grains or above per cubic meter of air, and the end date as the last day out of three consecutive days with a grass pollen count of 30 grass pollen grains or above per cubic meter of air.

Secondary Endpoints:

1. ARTSS of the six ARC symptoms (sneezing, rhinorrhea, nasal pruritus, nasal congestion, ocular pruritus and watery eyes)
2. Each of the six ARSS
3. ARMS and use of rescue medication
4. ACS

The study was initially designed to use the ARTSS as the primary endpoint. After Year 2, the primary endpoint was amended as the AASS, which includes both symptom (ARTSS) and medication scores (RMS).

### 6.3.9 Statistical Considerations & Statistical Analysis Plan

The study was initially designed to test the hypothesis that that the RTSS during the grass pollen season is no different in the treatment groups compared to the placebo group after three years of therapy. The primary endpoint was then redefined to test that the AASS during the grass pollen season is no different in the treatment groups compared to the placebo group.

For the initially stated endpoint, given an alpha of 0.05 and a common standard deviation of 3.106, the results of Study VO34.04 suggested that a sample size of 107 subjects per group would have a power of 80% to detect a mean difference of 1.2, that is, an average difference of 20% per symptom (1.2 / 6), between placebo and 300 IR in the average RTSS during the third pollen period while on treatment. Assuming a 20% screening failure rate and a 15% drop-out rate each year, 780 subjects were recruited in order to have 210 randomized subjects in each of the three treatment groups at the start of the study.

After redefining the endpoint, given an alpha of 0.05 and a common SD of 3.6, the results of Study VO34.04, suggested that a sample size of 144 subjects per group would have a power of 80% to detect a mean difference of 1.2 between placebo and 300 IR in the AASS during the third pollen period while on treatment. The screening failure rate was 13%, and the drop-out rate in each of the first two years of the study was 12%. Assuming this rate would be the same in the third year, then 633 randomized subjects would result

in approximately 144 subjects per group evaluable for sustained clinical effect during the third pollen period. Assuming a 12% drop-out rate for the fourth year, 127 subjects per group would provide a power of 75% to detect the same expected difference (1.2) with AASS for the post-treatment long-term efficacy.

### 6.3.10 Study Population and Disposition

#### 6.3.10.1 Protocol VO53.06 Populations Enrolled/Analyzed

The safety population included all subjects who received at least one dose of the investigational product.

The Full Analysis Set was considered primary for the efficacy analysis and included all subjects who received at least one dose of the investigational product and had at least one AAS during the pollen period while on treatment the corresponding year. The FAS included all subjects in the Safety Set who had at least one ASS during the Year 4 pollen period. The FAS is equal to the ITT population.

The PP population included all subjects who completed the study from Year 1 according to the protocol, had no major protocol violations, and who had either at least 14 valid ASS days or valid ASS days for at least 50% of the pollen period during the corresponding year's pollen period and had no major protocol deviations.

Subjects who were withdrawn from the study due to lack of efficacy or an AE related to the investigational product were included in the PP population if they were otherwise valid.

**Table 20. Disposition of Subjects in Protocol VO56.06**

	<b>Year 1</b>	<b>Year 2</b>	<b>Year 3</b>	<b>Year 4</b>	<b>Year 5</b>
Safety Population	633	508	465	442	382
PP Population	514	454	434	425	367
Full Analysis Set*	481	487	461	435	377

\*The Full Analysis Set (FAS) is the same as the Intent to Treat (ITT) set.

#### 6.3.10.1.1 Protocol VO53.06 Demographics

There were no significant differences between the study drug and placebo groups in the safety, ITT, or PP group among the following variables: gender, age, weight, height, or BMI.

#### 6.3.10.1.2 Protocol VO53.06 Medical/Behavioral Characterization of the Enrolled Population

##### Protocol VO53.06 Subject Criteria (relevant to allergic diseases and asthma)

The subjects enrolled were adults, 18-50 years of age who had allergic rhinoconjunctivitis due to grass pollen sensitivity. Subjects were required to have symptoms due to seasonal allergic rhinitis due to grass pollen allergy, and otherwise in general good health. The distribution among subjects in each dose group for use of drugs unrelated to ARC was equivalent between treatment groups.

One major variable that may affect efficacy and safety are whether the subject has asthma. Only asthmatic subjects with FEV1 > 80% of normal and who are not taking daily medication for asthma were randomized. Asthmatic subjects accounted for 16.1% of randomized subjects and was distributed equally among the three study groups..

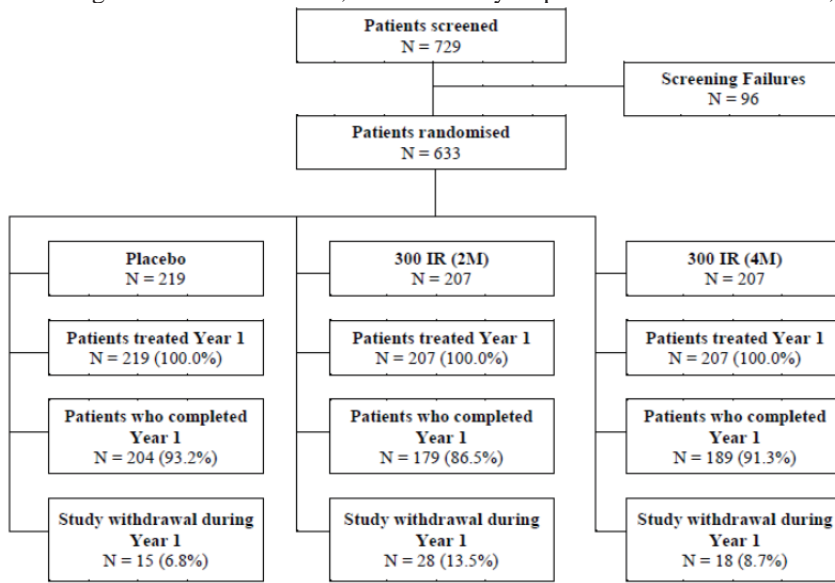
6.3.10.1.3 Protocol VO53.06 Subject Disposition

Subject Disposition for each year of the study is shown below.

**Figures 6-10. Subject disposition for each year of Protocol VO53.06**

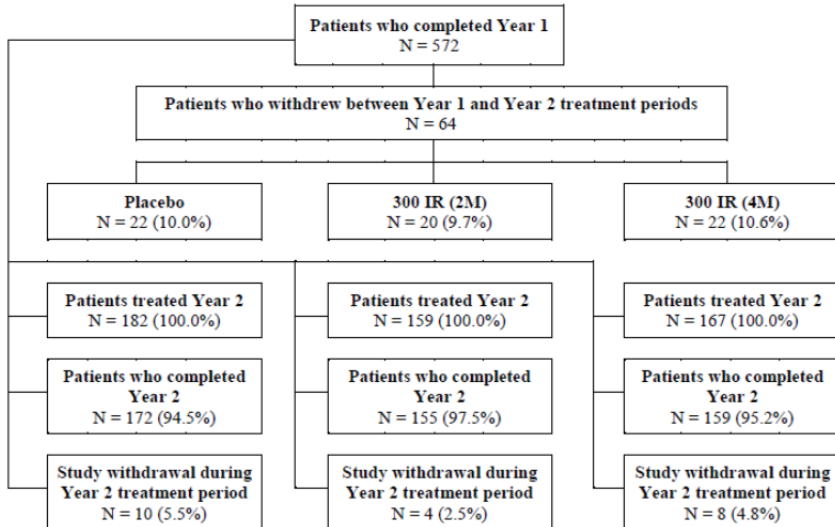
**Figure 6. Subject disposition Year 1**

from original BLA 125471/000; Clinical Study Report VO53 Years 1 to 4.06, p.83



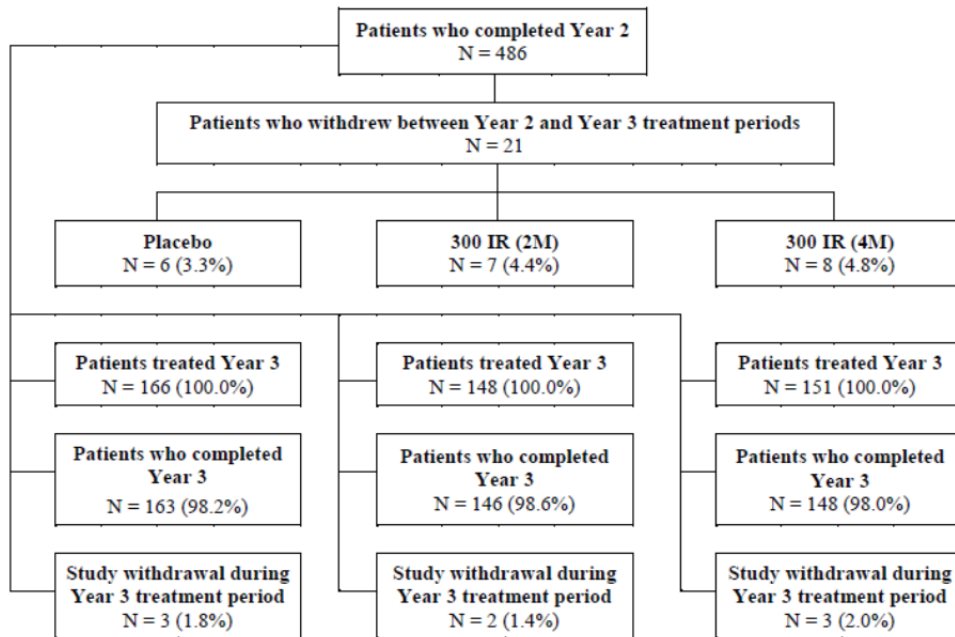
**Figure 7. Subject Disposition Year 2**

from original BLA 125471/000; Clinical Study Report VO53.06 Years 1 to 4, p.84



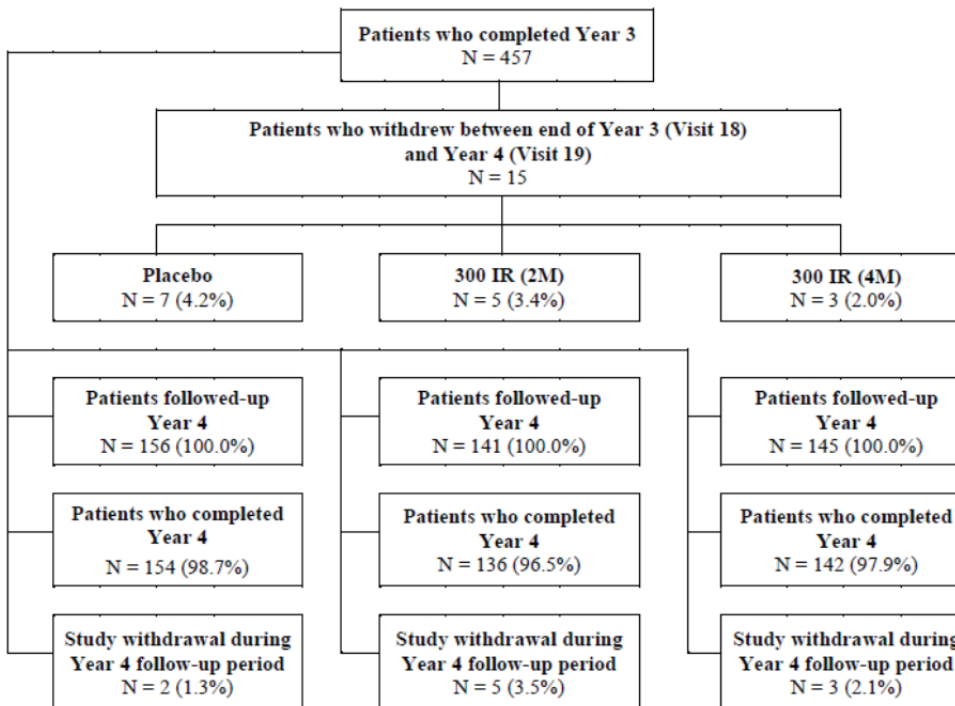
**Figure 8. Subject Disposition Year 3**

from original BLA 125471/000; Clinical Study Report VO53.06 Years 1 to 4, p.85



**Figure 9. Subject Disposition Year 4**

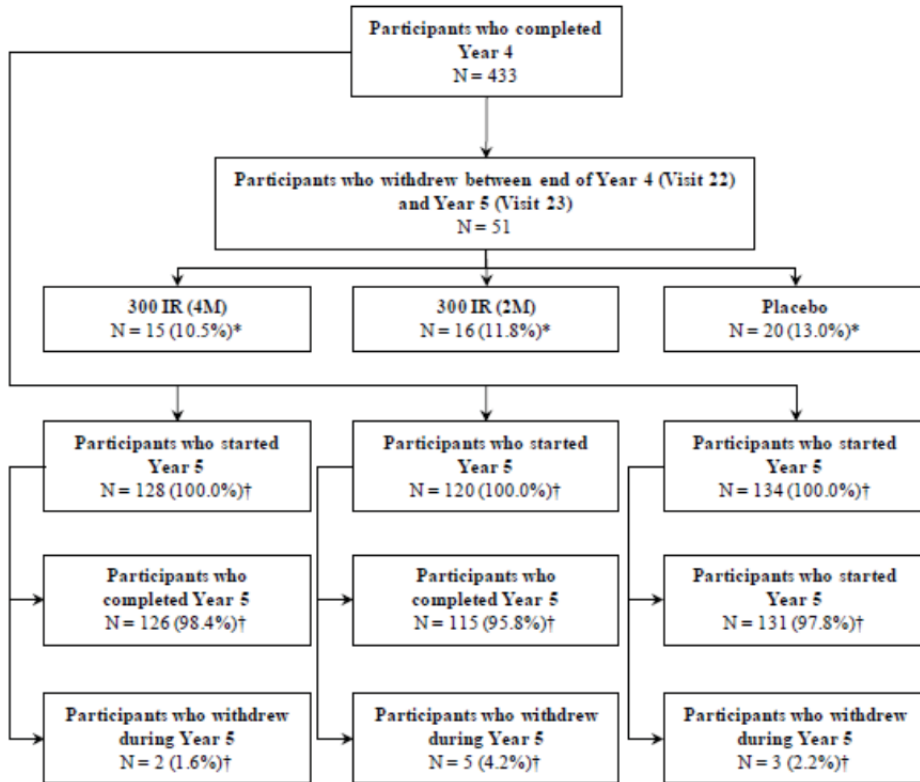
from original BLA 125471/000; Clinical Study Report VO53.06 Years 1 to 4, p.86





**Figure 10. Subject Disposition Year 5**

from original BLA 125471/000; Clinical Study Report VO53.06 Years 5, p.61

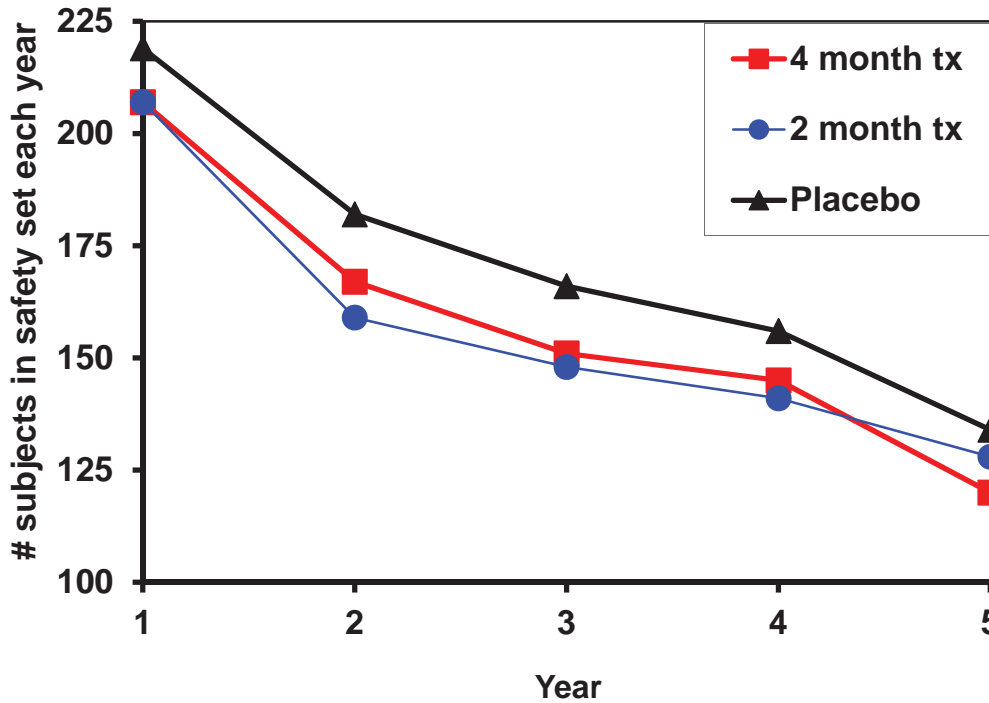


6.3.11 Protocol VO53.06 Efficacy Analyses

Figure 11 shows a comparable drop-out rate among the three study groups over the five years of study.

**Figure 11. Subject participation each year of VO53.06**

Adapted from original BLA 125471/000; Clinical Study Report VO53.06 Years 1 to 4, p.95



**6.3.11.1 Protocol VO53.06 Analyses of Primary Endpoint(s)**

The primary efficacy endpoint was the Average Adjusted Symptom Score (AASS) during the Year 3 pollen period while on treatment. The primary analysis was performed on the FAS after Year 3 (FAS<sub>Y3</sub>). As shown below, either treatment group (2M or 4M) met endpoint criteria for both point estimate, and 95% CI (4M point estimate: -34.9%; 95% CI -22.8%, -50.0%; 2M point estimate: -37.7%; 95% CI -22.3%, -53.0%)

**Table 21. AASS by ANCOVA FAS Year 3 of Protocol VO53.06**

from sBLA 125471/000; Clinical Study Report VO53.06 Years 1 to 4, p.11

Tx	N	Mean	Point Estimate	95% CI	P value	Relative LS mean difference (%)
Placebo	165	5.21				
300 IR (4M)	149	3.39	-1.82	-2.61, -1.02	<0.0001	-34.9
300 IR (2M)	147	3.25	-1.96	-2.76, -1.16	<0.0001	-37.6

Measurement of the sustained effect, as measured by the AASS during the Year 4 pollen period (FAS<sub>Y4</sub>) demonstrates that either treatment group (2M or 4M) met endpoint criteria for both point estimate, but the lower bound of the 95% CI was low for the 4M group (4M point estimate: -23.0%; 95% CI -5.2%, -59.4%; 2M point estimate: -28.6%; 95% CI -11.6%, -48.4%).

**Table 22. AASS by ANCOVA FAS Year 4 of Protocol VO53.06**  
from sBLA 125471/000; Clinical Study Report VO53.06 Years 1 to 4, p.117

Tx	N	Mean	Point Estimate	95% CI	P value	Relative LS mean difference (%)
Placebo	155	5.00				
300 IR (4M)	143	3.85	-1.14	-2.03, -0.26	0.0114	-22.9
300 IR (2M)	137	3.57	-1.43	-2.32, -0.53	0.0019	-28.5

Year 5 did not demonstrate benefit to the 300 IR (4M) group, and marginal benefit to the 300 IR (2M) group. Because the lower bound of the 95% CI does not exceed the acceptable 10% threshold, these data do not support sustained efficacy for two years post-treatment.

**Table 23. AASS by ANCOVA FAS Year 5**  
from sBLA 125471/000; Clinical Study Report VO53.06 Year 5, p.71

Tx	N	Mean	Point Estimate	95% CI	P value	Relative LS mean difference (%)
Placebo	133	4.51				
300 IR (4M)	127	3.86	-0.65	-1.60, 0.31	0.1854	-14.3
300 IR (2M)	117	3.49	-1.01	-1.99, -0.03	0.0433	-22.5

### 6.3.11.2 Protocol VO53.06 Analyses of Secondary Endpoints

#### Secondary Endpoint Set 1: Analysis of combined scores

##### *AASS in the Per Protocol Set*

Analysis of the AASS in the Per Protocol Set (PPS) for the complete pollen season yielded similar results in Years 1-4 to the FAS; there was benefit in third year of therapy that was marginally sustained into the fourth year. There was no sustained benefit in the PPS in AASS into Year 5 (second pollen season after discontinuing therapy).

##### *Average Combined Score of the FAS*

While the sponsors used the parameter of AASS as the primary endpoint of this study, CBER found the algorithm behind this calculation (Grouin et al. *Clin Exp Allergy* 4101282; 2011) to be unnecessarily complex. Instead, CBER relies on the average combined score (ACS), which is simply a non-weighted average of the ARTSS and the ARMS, in which the maximum value of each is 3. The maximum value of the ACS is 3.

As shown in below, the ACS was decreased in each of Years 1-4, although the lower bound of the 95% CI for Years 1 and 4 for the 300 IR (4M) treatment group Year 1 for the 300 IR (2M) treatment group were lower than the 10% threshold that CBER accepts as proof of efficacy. Because the primary endpoint for Year 5 was not met, the secondary endpoints for Year 5 are not discussed.

**Table 24. Average combined score (ACS) by ANCOVA FAS Year 5**

Adapted from Sponsor's and CBER briefing documents

	Treatment	n	LS Mean	Percent change LS Mean relative to placebo	Percent change LS Mean relative to placebo
Study VO53.06 Year 1 Treatment <sup>c,d</sup>	300 IR (4M)	188	0.56	-16.4%	-27.0%, -5.8%
Study VO53.06 Year 1 Treatment <sup>c,d</sup>	300 IR (2M)	188	0.53	-20.7%	-31.3%, -10.1%
Study VO53.06 Year 1 Treatment <sup>c,d</sup>	Placebo	205	0.67		
Study VO53.06 Year 2 Treatment <sup>c,d</sup>	300 IR (4M)	160	0.35	-38.0%	-53.4%, -22.6%
Study VO53.06 Year 2 Treatment <sup>c,d</sup>	300 IR (2M)	155	0.35	-38.3%	-54.0%, -22.7%
Study VO53.06 Year 2 Treatment <sup>c,d</sup>	Placebo	172	0.56		
Study VO53.06 Year 3 Treatment <sup>c,d</sup>	300 IR (4M)	149	0.31	-38.3%	-54.7%, -22.0%
Study VO53.06 Year 3 Treatment <sup>c,d</sup>	300 IR (2M)	147	0.29	-40.9%	-57.4%, -24.5%
Study VO53.06 Year 3 Treatment <sup>c,d</sup>	Placebo	165	0.50		
Study VO53.06 Year 4 Observation	300 IR (4M)	137	0.38	25.5%	-45.1, -5.9
Study VO53.06 Year 4 Observation	300 IR (2M)	143	0.35	31.4%	-51.1, 11.8
Study VO53.06 Year 4 Observation	Placebo	155	0.51		
Study VO53.06 Year 5 Observation	300 IR (4M)	127	0.27	-28.9%	-55.2%, -0.0%
Study VO53.06 Year 5 Observation	300 IR (2M)	117	0.27	-28.9	-57.9%, -0%
Study VO53.06 Year 5 Observation	Placebo	133	0.38		

**6.3.11.3 Protocol VO53.06 Subpopulation Analyses**

Not applicable

**6.3.11.4 Protocol VO53.06 Dropouts and/or Discontinuations**

Subjects who discontinued their participation in the study due to 'lack of efficacy' or an 'AE' were included in the PP analysis if they were otherwise valid. The tabular listing of subject withdrawals due to AE is found in Section 6.3.12.6.

### **6.3.11.5 Protocol VO53.06 Exploratory and Post Hoc Analyses**

#### Asthma Evaluation

Approximately 15-20% of subjects had mild asthma at baseline. Neither the severity nor the incidence of asthma was affected by the study drug.

### **6.3.12 Protocol VO53.06 Safety Analyses**

#### **6.3.12.1 Protocol VO53.06 Methods**

The safety of the investigational product was evaluated by monitoring the subject's AE profile from open-ended daily diary cards, physical examination findings (including vital signs) and by the assessment of routine clinical laboratory safety tests (performed at screening and end of treatment).

#### **6.3.12.2 Protocol VO53.06 Overview of Adverse Events**

As expected, the incidence of respiratory disorders in each study group was similar. There were more drug-related AE in the study drug groups, and more AE that led to study withdrawal in the study drug groups. There were no SAE or deaths. Most of the TEAE in the subjects in the treatment group that were considered related to the study drug were consistent with application site reactions (e.g. tongue, lips, or mouth edema; throat irritation) and were Grade 1 or 2 (mild or moderate severity that did not require discontinuation of therapy).

Table 25 shows the incidence of the most common AE in Year 1. For Years 2 and 3 of treatment, the overall rate of these common AE was dropped by about 20-25% of the previous year.

**Table 25. TEAE in  $\geq 3\%$  of ORALAIR subjects, either dose, Yr 1, Protocol VO53.06**

Adapted from sBLA 125471/000; Clinical Study Report VO53.06 Years 1 to 4, p.194-203

	Placebo N = 219	Placebo N = 219	300 IR (2M) N = 207	300 IR (2M) N = 207	300 IR (4M) N = 207	300 IR (4M) N = 207
	n	%	n	%	n	%
<b>Patients who had Year 1 TEAEs</b>	<b>173</b>	<b>79.0</b>	<b>168</b>	<b>81.2</b>	<b>183</b>	<b>88.4</b>
<b>Respiratory, thoracic and mediastinal disorders</b>	93	42.5	105	50.7	113	54.6
Throat irritation	12	5.5	43	20.8	53	25.6
Sneezing	41	18.7	34	16.4	31	15.0
Rhinorrhoea	36	16.4	31	15.0	32	15.5
Nasal discomfort	37	16.9	28	13.5	26	12.6
Nasal congestion	33	15.1	24	11.6	26	12.6
Cough	23	10.5	24	11.6	22	10.6
Pharyngolaryngeal pain	10	4.6	11	5.3	12	5.8
Rhinitis allergic	9	4.1	14	6.8	9	4.3
Pharyngeal oedema	1	0.5	9	4.3	9	4.3
<b>Gastrointestinal disorders</b>	40	18.3	104	50.2	126	60.9
Oral pruritus	28	12.8	68	32.9	89	43.0
Oedema mouth	3	1.4	16	7.7	20	9.7
Dyspepsia	0	0.0	7	3.4	11	5.3
Glossodynia	1	0.5	7	3.4	7	3.4
<b>Eye disorders</b>	75	34.2	66	31.9	53	25.6
Eye pruritus	39	17.8	32	15.5	27	13.0
Lacrimation increased	26	11.9	21	10.1	14	6.8
Conjunctivitis allergic	19	8.7	13	6.3	10	4.8
Conjunctivitis	11	5.0	16	7.7	12	5.8
<b>Infections and infestations</b>	75	34.2	51	24.6	63	30.4
Nasopharyngitis	29	13.2	12	5.8	28	13.5
Rhinitis	12	5.5	15	7.2	15	7.2
<b>Nervous system disorders</b>	33	15.1	24	11.6	20	9.7
Headache	30	13.7	21	10.1	17	8.2
<b>Ear and labyrinth disorders</b>	4	1.8	15	7.2	24	11.6
Ear pruritus	3	1.4	14	6.8	24	11.6

The following AE were also reported at a higher incidence in either treatment group compared to placebo: dysphonia, lip swelling, upper abdominal pain, swollen tongue, vomiting

### 6.3.12.3 Protocol VO53.06 Deaths

There were no deaths during the study Years 1-5.

### 6.3.12.4 Protocol VO53.06 Nonfatal Serious Adverse Events

There were no reports in either treatment group of severe anaphylaxis or anaphylactic shock or autoimmune disorders. During the 3 treatment periods, serious TEAE were reported by 12 subjects during Year 1 (2 from the placebo group), 4 (1 from the placebo group) subjects during Year 2 and 6 subjects during Year 3 (6 from the placebo group).

Three serious TEAE were considered drug-related by the Investigator. All occurred during the Year 1 treatment period in subjects in the 300 IR (4M) group. Two were application site reactions: one angioneurotic edema (Subject 0949/20) and one severe local allergic reaction (preferred term: hypersensitivity, [Subject 0419/07]). The third event, gastroenteritis, was concomitant with an infection. All these SAE resolved by the end of Year 1. Epinephrine was not required for any of these SAE.

*The reviewer concurs with these assessments of causality.*

In addition, an infant born to Subject 1054/03, 300 IR (2M) study group presented with a “Varosity of feet” associated with oligohydramnios and insufficient placenta. The drug exposure during the pregnancy was 12.7 weeks. The Investigator considered the event as unrelated to the study drug.

*The reviewer concurs that the SAE was unrelated to the study drug.*

There were no SAE in subsequent years that were considered related to the investigational product by the investigator, or by the reviewer.

All subjects who experienced SAE or recovered except:

- Subject 0310/09 (300 IR [2M] group) who experienced a “Testicular germ cell tumor mixed Stage II” in Year 1,
- Subject 0947/07 (Placebo group) who experienced an “Hepatitis B” in Year 1, and
- Subject 0844/03 (Placebo group) who experienced a “Lumbar vertebral fracture” in Year 4.

AE that precipitated withdrawal of subjects is reviewed comprehensively in Section 6.3.12.7.

#### **6.3.12.5 Protocol VO53.06 Adverse Events of Special Interest (AESI)**

None.

#### **6.3.12.6 Protocol VO53.06 Clinical Test Results**

There were no significant abnormalities in clinical laboratory tests or vital signs among the subjects in this study, with the exception of a elevated liver enzymes in the subject with Hepatitis B (placebo group) and one additional subject for which a cause was not assigned.

#### **6.3.12.7 Protocol VO53.06 Dropouts and/or Discontinuations**

Subjects who withdrew from the study in Years 1-3 are tabulated below. The reviewer agrees with the assessments of causality. Subjects in which causality was suspected or assigned are referenced in Table 31 and discussed below it. Table 31 and discussion of subjects are adapted from the original BLA 125471/0000 CSR VO53.06, p5176-5247

**Table 26. Subject withdrawals in Protocol VO53.06**

<b>Placebo Group</b>	<b>Diagnosis</b>	<b>Age/ gender</b>	<b>Year and Day of study drug administration</b>
Unrelated	Concussion	24F	Y2, D119
Unrelated	Renal Colic	33M	Y3, D146
Unrelated	Gastroenteritis	26F	Y3, D120
Unrelated	Asthma*	21F	Y3, D134
Unrelated	Hip Dysplasia	22M	Y2; D-22
Unrelated	Leg Fracture	36F	Y1, D60
Unrelated	Hepatitis B	36M	Y1, D50
Unrelated	Gingival Pain <sup>5</sup>	27F	Y1, D8
Possibly related or Related	Eczema	34M	Y1, D38
Possibly related or Related	Laryngeal edema <sup>30</sup>	33F	Y1, D53
<b>300 IR (2M) Study Drug Group</b>	<b>Diagnosis</b>	<b>Age/ gender</b>	<b>Year and Day of study drug administration</b>
Unrelated	Inguinal Hernia	38M	Y4
Unrelated	Testicular Tumor	24M	Y1, D82
Unrelated	Induced Abortion	31F	Y2, D69
Unrelated	Motor Vehicle Accident	53M	Y3, D102
Unrelated	Arthropathy	31M	Y2, D47
Unrelated	Knee injury	41M	Y1, D17
Unrelated	Knee injury	34F	Y3, D61
Possibly related or Related	Swollen Tongue <sup>6</sup>	26M	Y1, D2
Possibly related or Related	Adenovirus infection	29M	Y3, unknown
Possibly related or Related	Conjunctivitis <sup>11</sup>	34M	Y1, D34
Possibly related or Related	Pharyngeal edema <sup>13</sup>	22F	Y2, D1
Possibly related or Related	Chest Discomfort <sup>15</sup>	27F	Y1, D11
Possibly related or Related	Conjunctivitis	33M	Y1, D56
Possibly related or Related	Oral Pruritus <sup>20</sup>	26M	Y1, D1
Possibly related or Related	Gastrointestinal Pain <sup>22</sup>	43F	Y1, D32
Possibly related or Related	Dyspepsia	26M	Y1, D16
Possibly related or Related	Salivary gland enlargement <sup>24</sup>	44F	Y1, D5
Possibly related or Related	Depression	34F	Y2, none administered
Possibly related or Related	Lymphadenopathy	21F	Y1, D36
Possibly related or Related	Esophageal Pain <sup>26</sup>	23F	Y1, D10
Possibly related or Related	Oral pruritus <sup>28</sup>	34M	Y1, D2
Possibly related or Related	Liver Disorder (elevated enzymes) <sup>32</sup>	21F	Y1, D39
<b>300 IR (4M) Study Drug Group</b>	<b>Diagnosis</b>	<b>Age/ gender</b>	<b>Year and Day of study drug administration</b>
Unrelated	Appendicitis	23M	Y1, D51
Unrelated	Hypersensitivity <sup>1</sup>	25M	Y1, D1
Unrelated	Nasal Septum Deviation	29M	Y1; None administered
Unrelated	Eye Injury	40M	Y3, D88
Unrelated	Herniated Vertebral Disc	43M	Y1, D27
Unrelated	Gastroenteritis	43F	Y1, D100
Unrelated	Spinal cord injury	39M	Y2, D19



Unrelated	Familial Mediterranean Fever	30M	Y1, OTP
Unrelated	Cholelithiasis	35M	Y1, OTP
Unrelated	Head Contusion	21M	Y1, D19
Unrelated	Cervical Fracture	21M	Y1, D119
Unrelated	Angioneurotic edema <sup>2</sup>	30M	Y1, D1
Unrelated	Ectopic Pregnancy	34F	Y1, D43
Possibly related or Related	Oral Pruritus <sup>3</sup>	29M	Y1, D1
Possibly related or Related	Throat Irritation <sup>4</sup>	30M	Y1, D1
Possibly related or Related	Vomiting <sup>7</sup>	18F	Y1, D25
Possibly related or Related	Oral pruritus <sup>8</sup>	34M	Y1, D2
Possibly related or Related	Dysphagia	32M	Y1, D27
Possibly related or Related	Oral pruritus	31M	Y2, D1
Possibly related or Related	Glossodynia	44M	Y2, D13
Possibly related or Related	Asthma	47M	Y2, D141
Possibly related or Related	Abdominal Pain <sup>16</sup>	36F	Y1, D28
Possibly related or Related	Dyspnea <sup>17</sup>	31F	Y1, D2
Possibly related or Related	Mouth Edema <sup>19</sup>	18M	Y2, D1
Possibly related or Related	Oral Mucosal Blistering <sup>21</sup>	30F	Y2, D1
Possibly related or Related	Upper Abdominal Pain <sup>23</sup>	37M	Y2, D5
Possibly related or Related	Generalized Pruritus <sup>25</sup>	34F	Y2, D58
Possibly related or Related	Oral pruritus, esophageal pain, vomiting, tongue edema <sup>27</sup>	25M	Y1, D3
Possibly related or Related	Laryngeal edema <sup>29</sup>	23M	Y1, D53
Possibly related or Related	Dyspepsia <sup>31</sup>	34M	Y1, D58

\*Exercised induced asthma in a subject without previous history of asthma

<sup>1</sup>This 25-year-old female subject was randomized to 300 IR (4M) and first treated on 01 March 2007. On 01 March 2007 (Day 01 – Year 1), the subject was hospitalized due to severe hypersensitivity which began 5 minutes after administration of the investigational product (first dose) at 15:00. The symptoms were violent coughing and marked dyspnea with no itching and no problems with swallow reflex. On examination regular rhythm, no audible sounds of the heart and no additional sounds in the lungs were noted. Antihistamines, salbutamol and prednisolone were administered. The subject’s status stabilized and she was discharged from the emergency department after observation for a few hours on 01 March 2007. The subject was withdrawn from the study on 02 April 2007. Administration of the investigational product was discontinued on 01 March 2007 (Day 01). The subject recovered on 03 March 2007 (Day 03). This event was considered by the Investigator to be certainly related to the IMP.

<sup>2</sup>This 30-year-old male was randomized to 300 IR (4M) and first treated on 06 March 2007. On 06 March 2007 (Day 01 – Year 1) at 14:00, the subject received the first dose of the investigational product. Within 5 minutes after dosing the subject suffocated and his face turned red due to a lack of air. Severe laryngeal edema was noted but no facial swelling. A diagnosis of severe angioneurotic edema was made. The subject did not have a history of similar events. Prednisolone 60 mg was injected and within 30 minutes the event had totally resolved. Administration of the investigational product was permanently

discontinued and the subject withdrawn from the study on 06 March 2007. The subject recovered on 06 March 2007 (Day 01). This event was considered by the Investigator to be certainly related to the IMP.

<sup>3</sup>This 39-year-old male was randomized to 300 IR (4M) and first treated on 11 January 2007. From 11 January 2007 (Day 1 – Year 1) to 19 January 2007 the subject presented with moderate oral pruritus. On 20 January 2007 (Day 10) the subject presented with mild oral pruritus. Administration of the investigational product was permanently discontinued and the subject was withdrawn from the study on 24 July 2007. The subject recovered on 24 July 2007 (Day 195). These events were considered by the Investigator to be certainly related to the IMP

<sup>4</sup>This 30-year-old male was randomized to 300 IR (4M) and first treated on 09 January 2007. On 09 January 2007 (Day 01 – Year 1), the subject presented with throat irritation. Administration of the investigational product was permanently discontinued and the subject was withdrawn from the study on 24 July 2007. The subject recovered on 09 July 2007 (Day 182). This event was considered by the Investigator to be certainly related to the IMP.

<sup>5</sup>This 27-year-old female subject, was randomized to Placebo and first treated on 01 February 2007. On 07 February 2008 (Day 08 – Year 2), the subject presented with severe gingival pain. Consequently, Advil (ibuprofen) 400 mg orally was administered from 09 February 2008 to 10 February 2008. Administration of the investigational product was permanently discontinued and the subject was withdrawn from the study on 12 February 2008. As the symptoms did not resolve, the event was ongoing at her withdrawal from the study. This event was considered by the Investigator to be certainly related to the IMP.

<sup>6</sup>This 26-year-old male was randomized to 300 IR (2M) and first treated on 22 February 2007. On 03 April 2007 (Day 02 – Year 1, while subject took active treatment), the subject presented with a swollen tongue. Administration of the investigational product was permanently discontinued and the subject was withdrawn from the study on 06 June 2007. The subject recovered on 20 April 2007 (Day 19). This event was considered by the Investigator to be certainly related to the IMP.

<sup>7</sup>This 18-year-old female was randomized to 300 IR (4M) and first treated on 26 January 2007. On 19 February 2007 (Day 25 – Year 1), the subject presented with intermittent vomiting. Administration of the investigational product was permanently discontinued and the subject was withdrawn from the study on 22 February 2007. The subject recovered on the same day. This event was considered by the Investigator to be certainly related to the IMP.

<sup>8</sup>This 34-year-old male was randomized to 300 IR (4M) and first treated on 30 January 2007. On 31 January 2007 (Day 02 – Year 1) the subject presented with oral pruritus. Administration of the investigational product was permanently discontinued and the subject was withdrawn from the study on 11 April 2007. The subject recovered on 20 February 2007 (Day 22). This event was considered by the Investigator to be certainly related to the IMP.

<sup>9</sup>This 32-year-old male was randomized to 300 IR (4M) and first treated on 25 January 2007. On 20 February 2007 (Day 27 – Year 1), the subject presented with dysphagia. Administration of the investigational product was permanently discontinued and the subject was withdrawn from the study on 22 March 2007. The subject recovered on 12 March 2007 (Day 47). This event was considered by the Investigator to be certainly related to the IMP.

<sup>9</sup>This 34-year-old male was randomized to 300 IR (2M) and first treated on 06 February 2007. On 16 May 2007 (Day 34 – Year 1, while subject took active treatment), the subject presented with severe conjunctivitis. Administration of the investigational product was permanently discontinued and the subject was withdrawn from the study on 16 May 2007. The subject recovered on 13 June 2007 (Day 62). This event was considered by the Investigator to be possibly related to the IMP.

<sup>12</sup>This 41-year-old male was randomized to 300 IR (4M) and first treated on 13 February 2007. On 07 February 2008 (Day 01 – Year 2), the subject presented with oral pruritus. Administration of the investigational product was permanently discontinued and the subject was withdrawn from the study on 10 April 2008. The subject recovered on 09 April 2008 (Day 63). This event was considered by the Investigator to be certainly related to the IMP.

<sup>13</sup>This 22-year-old female was randomized to 300 IR (2M) and first treated on 09 February 2007. On 04 April 2008 (Day 01 – Year 2, while subject took active treatment), the subject presented with pharyngeal edema. Administration of the investigational product was permanently discontinued and the subject was withdrawn from the study on 15 May 2008. The subject recovered on 24 April 2008 (Day 21). This event was considered by the Investigator to be certainly related to the IMP.

<sup>14</sup>This 44-year-old male subject was randomized to 300 IR (4M) and first treated on 13 February 2007. On 16 February 2008 (Day 13 – Year 2), the subject presented with glossodynia. Administration of the investigational product was permanently discontinued and the subject was withdrawn from the study on 10 March 2008. The subject recovered on 26 February 2008 (Day 23). This event was considered by the Investigator to be certainly related to the IMP.

<sup>15</sup>This 27-year-old female was randomized to 300 IR (2M) and first treated on 13 February 2007. On 20 April 2007 (Day 11 – Year 1, while subject took active treatment), the subject presented with chest discomfort. Consequently, Alnok (cetirizine) 10 mg orally from 12 April 2007 to 10 May 2007 was administered. Administration of the

investigational product was permanently discontinued and the subject was withdrawn from the study on 10 May 2007. The subject recovered on 10 May 2007 (Day 31). This event was considered by the Investigator to be certainly related to the IMP.

<sup>16</sup>This 35-year-old female subject was randomized to 300 IR (4M) and first treated on 16 February 2007. On 15 March 2007 (Day 28 – Year 1), the subject presented with abdominal pain. Consequently, Asytec (cetirizine) 10 mg orally was administered from 15 April 2007. Administration of the investigational product was temporarily discontinued and the subject was withdrawn from the study on 16 May 2007. The subject recovered on 10 May 2007 (Day 84). This event was considered by the Investigator to be certainly related to the IMP.

<sup>17</sup>This 31-year-old male was randomized to 300 IR (4M) and first treated on 19 February 2007. On 20 February 2007 (Day 02 – Year 1), the subject presented with dyspnea. Consequently, Bricanyl (terbutaline) 1 mg inhaled was administered starting from an unknown date. Administration of the investigational product was permanently discontinued and the subject was withdrawn from the study on 21 May 2007. The subject recovered on 10 May 2007 (Day 81). This event was considered by the Investigator to be probably/likely related to the IMP.

<sup>19</sup>This 18-year-old male was randomized to 300 IR (4M) and first treated on 22 February 2007. On 13 February 2008 (Day 01 – Year 2), the subject presented with mouth oedema. Administration of the investigational product was permanently discontinued and the subject was withdrawn from the study on 25 April 2008. The subject recovered on 02 March 2008 (Day 19). This event was considered by the Investigator to be certainly related to the IMP.

<sup>20</sup>This 26-year-old male was randomized to 300 IR (2M) and first treated on 24 January 2007. On 20 March 2007 (Day 01 – Year 1, while subject took active treatment), the subject presented with oral pruritus. Administration of the investigational product was permanently discontinued and the subject was withdrawn from the study on 24 July 2007. The subject recovered on 10 July 2007 (Day 113). This event was considered by the Investigator to be probably/likely related to the IMP.

<sup>21</sup>This 30-year-old female was randomized to 300 IR (2M) and first treated on 30 January 2007. On 28 January 2008 (Day 01 – Year 2, while subject took Placebo), the subject presented with oral mucosal blistering. Consequently, Lorano (loratadine) 10 mg orally on 18 February 2008 and 20 March 2008 was administered. Administration of the investigational product was permanently discontinued and the subject was withdrawn from the study on 25 March 2008. The subject recovered on 24 March 2008 (Day 57). This event was considered by the Investigator to be certainly related to the IMP.

<sup>22</sup>This 43-year-old female was randomized to 300 IR (2M) and first treated on 31 January 2007. On 21 April 2007 (Day 32 – Year 1, while subject took active treatment), the subject presented with gastrointestinal pain. Administration of the investigational product was permanently discontinued and the subject was withdrawn from the study on 05 September 2007. The subject recovered on 11 July 2007 (Day 113). This event was considered by the Investigator to be probably/likely related to the IMP.

<sup>23</sup>This 37-year-old male was randomized to 300 IR (4M) and first treated on 26 January 2007. From 25 January 2008 to 06 February 2008 (Day 5 to Day 17 – Year 2), the subject presented with upper abdominal pain. On 13 February 2008 (Day 24 – Year 2), the subject presented again with upper abdominal pain. Administration of the investigational product was temporarily discontinued. Consequently, Nexium (esomeprazole) 20 mg orally from 06 February 2008 to 16 February 2008 and from 18 February 2008 to 22 February 2008 was administered. Administration of the investigational product was permanently discontinued and the subject was withdrawn from the study on 17 March 2008. The subject recovered on 20 February 2008 (Day 31). Both events were considered by the Investigator to be probably/likely related to the IMP.

<sup>24</sup>This 44-year-old female was randomized to 300 IR (2M) and first treated on 22 January 2007. On 23 March 2007 (Day 05 – Year 1, while subject took active treatment), the subject presented with salivary gland enlargement. Administration of the investigational product was permanently discontinued and the subject was withdrawn from the study on 07 May 2007. The subject recovered on 03 May 2007 (Day 46). This event were considered by the Investigator to be certainly related to the IMP.

<sup>25</sup>This 34-year-old female was randomized to 300 IR (4M) and first treated on 12 February 2007. On 18 March 2008 (Day 58 – Year 2), the subject presented with generalized pruritus. Consequently, cetirizine 10 mg orally was administered from March 2008 to May 2008. Administration of the investigational product was permanently discontinued and the subject was withdrawn from the study on 14 May 2008. The subject recovered during May 2008. This event were considered by the Investigator to be certainly related to the IMP.

<sup>26</sup>This 23-year-old female was randomized to 300 IR (2M) and first treated on 01 February 2007. On 06 April 2007 (Day 10 – Year 1, while subject took active treatment), the subject presented with esophageal pain. Consequently, Claritine (loratadine) 10 mg orally was administered from 05 April 2007 to 10 April 2007. Administration of the investigational product was permanently discontinued and the subject was withdrawn from the study on 11 April 2007. The subject recovered on 10 April 2007 (Day 14). This event were considered by the Investigator to be certainly related to the IMP.

<sup>27</sup>This 25-year-old male was randomized to 300 IR (4M) and first treated on 02 February 2007. On 04 February 2007 (Day 03–Year 1), the subject presented with oral pruritus and esophageal pain. On 08 February 2007 (Day 07) the subject presented with vomiting. On 09 February 2007 (Day 08) the subject presented with tongue edema. Administration of the investigational product was permanently discontinued and the subject was withdrawn

from the study on 09 February 2007. The subject recovered from vomiting on 08 February 2007 (Day 07) and from oral pruritus, esophageal pain and tongue edema on 10 February 2007 (Day 09). All these events were considered by the Investigator to be certainly related to the IMP.

<sup>28</sup>This 34-year-old male was randomized to 300 IR (2M) and first treated on 15 February 2007. On 13 April 2007 (Day 02 – Year 1, while subject took active treatment), the subject presented with oral pruritus. Administration of the investigational product was permanently discontinued and the subject was withdrawn from the study on 24 May 2007. The subject recovered on 28 April 2007 (Day 17). This event was considered by the Investigator to be certainly related to the IMP.

<sup>29</sup>This 23-year-old male was randomized to 300 IR (4M) and first treated on 26 February 2007. On 19 April 2007 (Day 53 – Year 1), the subject presented with laryngeal edema. Administration of the investigational product was permanently discontinued and the subject was withdrawn from the study on 30 May 2007. The subject recovered on 22 April 2007 (Day 56). This event was considered by the Investigator to be probably/likely related to the IMP.

<sup>30</sup>This 33-year-old female was randomized to Placebo and first treated on 06 March 2007. On 27 April 2007 (Day 53–Year 1), the subject presented with laryngeal edema. Administration of the investigational product was permanently discontinued and the subject was withdrawn from the study on 31 May 2007. The subject recovered on 27 April 2007 (Day 53). This event was considered by the Investigator to be certainly related to the IMP.

<sup>31</sup>This 34-year-old male was randomized to 300 IR (4M) and first treated on 19 February 2007. On 17 April 2007 (Day 58 – Year 1), the subject presented with dyspepsia. Administration of the investigational product was permanently discontinued and the subject was withdrawn from the study on 31 July 2007. The subject recovered on 17 July 2007 (Day 149). This event was considered by the Investigator to be possibly related to the IMP.

<sup>32</sup>This 21-year-old female subject was randomized to 300 IR (2M) and first treated on 19 January 2007. On 26 April 2007 (Day 39 – Year 1, while subject took active treatment), the subject presented with a liver disorder. The following laboratory values were reported on 15 December 2006 and 10 May 2007, respectively: AST 15 IU/L and 104 IU/L (range 10 to 36 IU/L) and ALT 9 IU/L and 271 IU/L (range 6 to 37 IU/L). Administration of the investigational product was permanently discontinued and the subject was withdrawn from the study on 10 May 2007. The event was ongoing at the withdrawal from the study. This event was considered by the Investigator to be possibly related to the IMP.

### 6.3.13 Protocol VO53.06 Reviewer's conclusions:

The primary efficacy endpoint was the Average Adjusted Symptom Score (AASS) during the Year 3 pollen period while on treatment. Either treatment group (2M or 4M) met endpoint criteria for both point estimates, and 95% CI (4M point estimate: -34.9%; 95% CI -22.8%, -50.0%; 2M point estimate: -37.7%; 95% CI -22.3%, -53.0%). Therefore, the study met its primary endpoint.

The AASS during the Year 4 pollen period (FAS<sub>Y4</sub>) demonstrates that the point estimate of either treatment group (2M or 4M) was lower than placebo, but the lower bound of the 95% CI was not sufficient for the 4M group (4M point estimate: -23.0%; 95% CI -5.2%, -59.4%; 2M point estimate: -28.6%; 95% CI -11.6%, -48.4%). Therefore, only the 300 IR (2M) study group met this endpoint for sustained efficacy for Year 4. Neither group met the endpoint for sustained efficacy for Year 5.

There were more withdrawals due to TEAE in the study drug groups than the placebo group. Most local AE occurred early (most on Day 1), were local events (e.g. throat, mouth, larynx) and were mild to moderate in severity. Gastrointestinal AE that were TEAE occurred later during therapy. The two SAE that were related to study drug occurred on Day 1 of therapy.

### 6.4 Trial #4 (Supportive for safety only)

*Protocol VO60.08: A randomized, double-blind, placebo-controlled, multi-national, Phase III study of the efficacy and safety of 300 IR sublingual immunotherapy (SLIT), starting 2 months before the grass pollen season, administered as allergen-based tablets once daily to subjects suffering from grass pollen rhinoconjunctivitis (with or without asthma)*

#### 6.4.1 Protocol VO60.08 Objectives (Primary, Secondary, etc)

##### Primary Objective:

To assess the efficacy of sublingual tablets of grass pollen allergen extract on the Average Adjusted Symptom Score (AASS), which is a score adjusting the rhinoconjunctivitis Total Symptom Score (RTSS) based on the rescue medication use.

##### Secondary Objectives:

- The AASS on non-primary efficacy analysis sets and/or other evaluation period.
- The Average Rhinoconjunctivitis Total Symptom Score (ARTSS) of the six rhinoconjunctivitis symptoms sneezing, rhinorrhea, nasal pruritus, nasal congestion, ocular pruritus and watery eyes.
- Each of the six individual Average Rhinoconjunctivitis Symptom Scores (ARSSs).
- The Average Rescue Medication Score (ARMS) and use of rescue medication (antihistamine [oral form or/and eye drops], nasal corticosteroid and oral corticosteroid).
- The Average Combined Score (ACS) which is a score taking into account the RTSS and Rescue Medication Score (RMS).

- The proportion of symptom-controlled days (PSCD).
- The global evaluation of the efficacy of sublingual tablets of grass pollen allergen extract by the subject.

#### 6.4.2 Design Overview

This is a single year, RDBPC trial to evaluate the safety and efficacy of ORALAIR, 300 IR per day, beginning two months prior to the grass pollen season (GPS) and extending through the GPS. The design of the study is identical to the first year of Study VO53.06 with the following exceptions:

- The study is one year of treatment rather than three, and observation is for one GPS
- The age range is 12-50 years of age rather than 18-50 years of age
- Treatment prior to the GPS was for 2 months; there was no 4 month pre-treatment group

#### Protocol VO60.08 Study Design

Phase: Phase 3, RDBPC  
Subject Population: Adults ages 12 to 50 years (inclusive)  
Randomization/Blinding: RDBPC  
Location of Study: France, the Czech Republic (only subjects 18-50), Italy, Spain and The Netherlands  
Number of Study Centers: 38

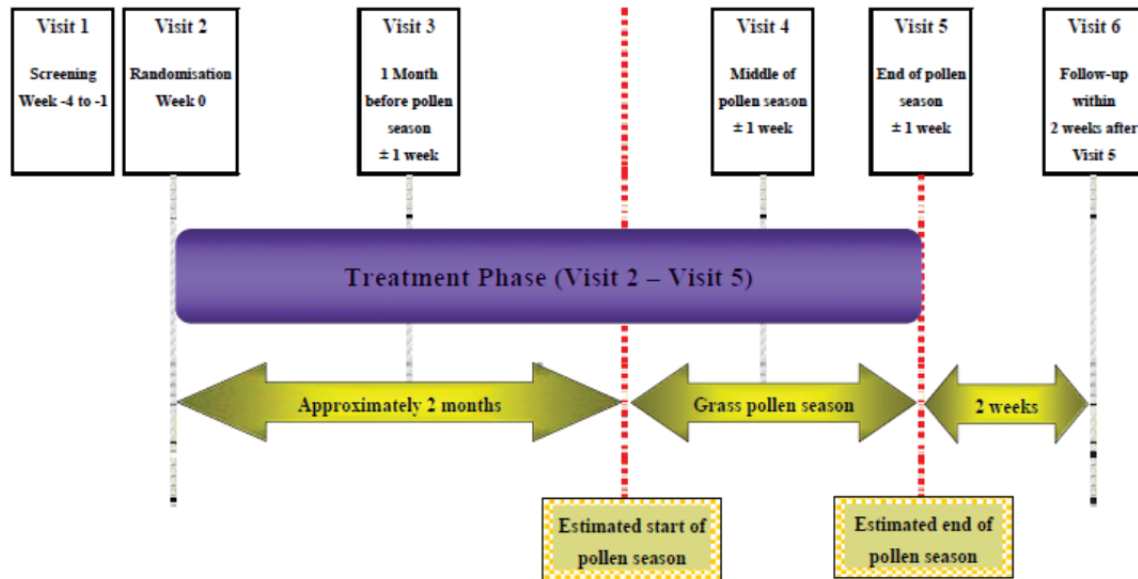
#### Protocol VO60.08 Duration of Study:

Total Study: 18 February 2009 to 31 August 2009  
Screening: Approximately 4 weeks  
Treatment: Approximately 4 months  
Follow-up: Within two weeks of the end of GPS



**Figure 12. Design of Protocol VO60.08**

from sBLA 125471/000; Clinical Study Report VO60.08, p.31



Reviewer Comment

The study was well designed to meet its objectives, but failed to demonstrate efficacy of the study drug.

6.4.3 Protocol VO60.08 Population

Identical to VO53.06, except the age of subjects ranges from 12-50 years of age rather than 18-50.

6.4.4 Protocol VO60.08 Study Treatments or Agents Mandated by the Protocol

The formulation of study drug and placebo tablets is identical to previous studies. Batch numbers for the study drug and placebo were P0238 and P0235, respectively. Both were manufactured in May 2008, and both expired in April, 2010.

6.4.5 Protocol VO60.08 Directions for Use

Subjects were instructed to leave the tablet(s) under the tongue until complete dissolution before swallowing.

6.4.6 Sites and Centers

The Principal Coordinator of the study was Dr. Oliveir de Beaumont of Stallergenes. There were between 38 study centers in four EU countries (Czech Republic, Spain, France, and Italy).

The Contract Research Organization (CRO) that managed this study was (b)(4). Subsidiaries of (b)(4) wrote the protocol, developed the CRF, and managed the data, including writing, CRF development, data management, and statistical analysis. Pharmacovigilance, quality assurance and regulatory activities were managed by (b)(4).

#### 6.4.7 Protocol VO60.08 Surveillance/Monitoring

The safety of the investigational product was evaluated by monitoring AE through the use of daily diary cards (passive) and history/physical examinations (active) during the study visits. A DSMB monitored the study and made the decision to continue with the study after the first year. The CRF forms for active surveillance were included in the IND and BLA submissions, and were appropriate.

#### 6.4.8 Protocol VO60.08 Endpoints and Criteria for Study Success

Primary and secondary endpoints are essentially identical to those of Protocol VO53.06.

#### 6.4.9 Protocol VO60.08 Statistical Considerations & Statistical Analysis Plan

The null hypothesis is essentially identical to that of Protocol VO53.06.

#### 6.4.10 Protocol VO60.08 Study Population and Disposition

##### **6.4.10.1 Protocol VO60.08 Populations Enrolled/Analyzed**

The FAS, PPS, and the Safety Sets are identical to those described in VO53.06.

##### *6.4.10.1.1 Protocol VO60.08 Demographics*

There were no significant differences between the study drug and placebo groups in the safety, ITT, or PP group among the following variables: gender, age, weight, height, or BMI.

##### *6.4.10.1.2 Protocol VO60.08 Medical/Behavioral Characterization of the Enrolled Population*

The subjects enrolled were adolescents and adults, 12-50 years of age who had allergic rhinoconjunctivitis due to grass pollen sensitivity. Subjects were required to have symptoms due to seasonal allergic rhinitis due to grass pollen allergy, and otherwise in general good health. The distribution among subjects in each dose group for use of drugs unrelated to ARC was equivalent between treatment groups.

Presence of asthma was a major variable that may affect efficacy and safety. Only asthmatic subjects with FEV1 > 80% of normal and who were not taking daily medication were randomized. Asthmatic subjects accounted for 25.9% and 32.0% of subjects in the study drug and placebo group, respectively.

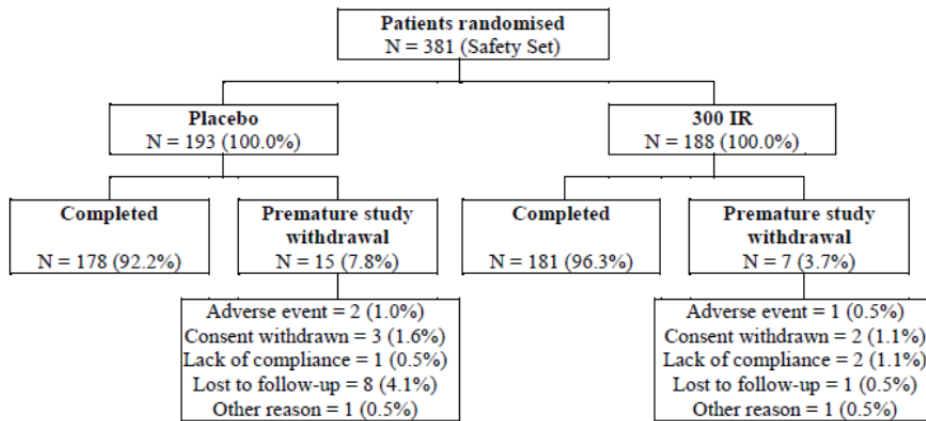
A second major variable is whether the subjects were sensitized only to grass pollen. Since the subjects were skin-tested with a 5-mix grass pollen extract, subjects who were sensitive to any one or more grass pollens were all considered “mono-sensitized.” “Poly-sensitized” subjects were those who were also allergic to weeds, trees, and other environmental allergens. Mono-sensitized subjects accounted for 40.0% and 41.6% of subjects in the study drug and placebo group, respectively.

Drugs in the ATC Class “Respiratory System” were the most common concomitant medications. These included topical and systemic antihistamines, topical decongestants, all of which are used to treat ARC. Inhalant beta-adrenergics were used by 15.0% and 17.0% of subjects in the study drug and placebo group, respectively.

6.4.10.1.3 Protocol VO60.08 Subject Disposition

**Figure 13. Study population and disposition for Protocol VO60.08**

from original BLA 125471/000; Clinical Study Report VO60.08, p.80



N = number of patients, % = percentage of patients, IR = index of reactivity.  
Source: Section 14, Table 14.1.1/1 and Table 14.1.1/2.

6.4.11 Protocol VO60.08 Efficacy Analyses

6.4.11.1 Protocol VO60.08 Analyses of Primary Endpoint(s)

As shown below, Protocol VO60.08 did not meet its primary endpoint.

**Table 27. AASS in study drug and placebo groups, Protocol VO60.08**

from original BLA 125471/000; Clinical Study Report VO60.08, p.95

Tx	N	Mean	Point Estimate	95% CI	P value	Relative LS mean difference (%)
Placebo	184	6.07				
300 IR	178	5.58	-0.49	-1.30, 0.32	0.2344	-8.1

6.4.11.2 Protocol VO60.08 Analyses of Secondary Endpoints

Because this study did not meet its primary endpoint, secondary endpoints were not reviewed.

6.4.11.3 Protocol VO60.08 Subpopulation Analyses

Not applicable.

#### **6.4.11.4 Protocol VO60.08 Dropouts and/or Discontinuations**

Because this study did not meet its primary endpoint, the effect of dropouts and/or discontinuations on efficacy assessment were not reviewed.

#### **6.4.11.5 Protocol VO60.08 Exploratory and Post Hoc Analyses**

Because this study did not meet its primary endpoint, exploratory endpoints were not reviewed.

### **6.4.12 Safety Analyses**

#### **6.4.12.1 Protocol VO60.08 Methods**

The safety of the investigational product was evaluated by monitoring the subject's AE profile from daily diary cards, physical examination findings (including vital signs) and by the assessment of routine clinical laboratory safety tests (performed at screening and end of treatment).

#### **6.4.12.2 Protocol VO60.08 Overview of Adverse Events**

As expected, the incidence of respiratory disorders in each study group was similar. There were more drug-related AE in the treatment group, and more AE that led to study withdrawal in the treatment group. There were no SAE or deaths. Most of the TEAE in the subjects in the treatment group that were considered related to the study drug were consistent with application site reactions (e.g. tongue, lips) and were Grade 1 or 2 (mild or moderate severity that did not require discontinuation of therapy).

**Table 28. Incidence of TEAE in Protocol VO60.08**

from original BLA 125471/000; Clinical Study Report VO60.08, p.134

Number of subjects with	Treatment Group Placebo N = 193	Treatment Group Placebo N = 193	Treatment Group Placebo N = 193	Treatment Group 300 IR N = 188	Treatment Group 300 IR N = 188	Treatment Group 300 IR N = 188
	n	%	m	n	%	m
At least one TEAE	117	60.6	248	134	71.3	396
At least one local TEAE expected with SLIT	34	17.6	40	107	56.9	193
At least one systemic TEAE expected with SLIT	50	25.9	66	45	23.9	62
At least one drug-related TEAE	26	13.5	39	102	54.3	184
At least one local drug-related TEAE expected with SLIT	15	7.8	17	94	50.0	156
At least one systemic drug-related TEAE expected w/SLIT	6	3.1	8	15	8.0	16
At least one serious TEAE	1	0.5	1	1	0.5	1
At least one serious drug-related TEAE	0	0.0	0	0	0.0	0
An AE leading to premature investigational product discontinuation	2	1.0	2	1	0.5	3
An AE leading to premature study withdrawal	2	1.0	2	1	0.5	1
An AE leading to death	0	0.0	0	0	0.0	0

**Table 29. Incidence of TEAE that occurred in at least 5% of subjects in Protocol VO68.08**

From original BLA 125471/000; Clinical Study Report VO60.08, p.136 of 7896 System Organ Class Preferred Term	Treatment Group Placebo N = 193	Treatment Group Placebo N = 193	Treatment Group Placebo N = 193	Treatment Group 300 IR N = 188	Treatment Group 300 IR N = 188	Treatment Group 300 IR N = 188
	n	%	m	n	%	m
Patients with TEAEs	117	60.6	248	134	71.3	396
Gastrointestinal disorders	25	13	29	86	45.7	151
Oral pruritus	5	2.6	5	60	31.9	70
Edema mouth	0	0.0	0	13	6.9	13
Respiratory, thoracic and mediastinal	44	22.8	58	59	31.4	77
Throat irritation	9	4.7	9	31	16.5	34
Asthma	12	6.2	12	8	4.3	9
Cough	11	5.7	11	9	4.8	9
Nervous system disorders	35	18.1	54	37	19.7	54
	32	16.6	49	32	17.0	47
Infections and infestations	38	19.7	40	28	14.9	33
	6	3.1	7	11	5.9	13

#### **6.4.12.3 Protocol VO60.08 Deaths**

There were no deaths.

#### **6.4.12.4 Protocol VO60.08 Nonfatal Serious Adverse Events**

A 20 year old female was given her first dose of study drug (ORALAIR, 300 IR) on 27 March 2009. She presented with intermittent severe oropharyngeal discomfort and generalized pruritus. The investigational product was permanently discontinued and the subject was withdrawn from the study. The investigator considered the SAE to be related to the study drug.

*The reviewer concurs that the SAE is related to the study drug.*

Two subjects reported SAEs, Subject 0107/02 in 300 IR reported a tibia fracture and Subject 0329/02 in Placebo reported a shoulder dislocation. Both SAEs were considered to be not related to the investigational product by the Investigators.

*The reviewer concurs that the SAEs are not related to the investigational product.*

#### **6.4.12.5 Protocol VO60.08 Adverse Events of Special Interest (AESI)**

None.

#### **6.4.12.6 Protocol VO60.08 Clinical Test Results**

There were no significant abnormalities in clinical laboratory tests or vital signs in this study.

#### **6.4.12.7 Protocol VO60.08 Dropouts and/or Discontinuations**

In addition to the non-fatal SAE listed in Section 6.4.12.4, two subjects withdrew to AE. One subject was withdrawn due to abdominal pain caused by an ovarian cyst. This was considered unrelated to the study drug.

*The reviewer agrees that this AE is related to the investigational product.*

#### **6.4.13 Protocol VO53.06 Reviewer's conclusions:**

Protocol VO53.06 did not meet its primary efficacy endpoint. The safety profile of ORALAIR in this study is consistent with the other studies reviewed in this document: local AE that are usually mild to moderate in intensity. The SAE occurred on Day 1 of therapy.

### **6.5 Trial #5 (Supportive for Efficacy and Safety)**

*Protocol VO56.07: A randomized, double-blind, in parallel groups, placebo controlled mono-centre, Phase I study to assess after allergen challenge in an allergen exposition chamber the effect and its time course of sublingual immunotherapy (SLIT) administered as 300IR allergen-based tablets once daily to adults suffering from grass pollen rhinoconjunctivitis.*

### 6.5.1 Protocol VO56.07 Objectives (Primary, Secondary, etc)

Primary Objective: To assess the effect of grass pollen extract SLIT tablets on the Average Rhinoconjunctivitis Total Symptom Score (ARTSS) of the six symptoms: sneezing, rhinorrhea, nasal pruritus, nasal congestion, ocular pruritus and watery eyes, at endpoint (after four months of treatment or, in case of withdrawal, during the last available challenge) compared to placebo, in response to grass pollen challenge in subjects suffering from Seasonal Allergic Rhinoconjunctivitis (SAR) due to grass pollen.

#### Secondary Objectives:

1. To assess the effect of grass pollen extract SLIT tablets on the ARTSS after one week, one and two months of treatment, compared to placebo, in response to grass pollen challenge in subjects suffering from SAR due to grass pollen.
2. To assess the onset of action of treatment.
3. To assess the effect of grass pollen extract SLIT tablets on the following parameters after one week and one, two, four months of treatment and at endpoint compared to placebo, in response to grass pollen challenge in subjects suffering from SAR due to grass pollen:
  - Each average individual symptom score (ISS).
  - The nasal airflow as measured by Active Anterior Rhinomanometry (AAR).
  - The nasal secretion weight.
4. To assess the effect of grass pollen extract SLIT tablets on cutaneous reactivity after one, two, four months of treatment and at endpoint compared to placebo.
5. To document the safety of the treatment.

### 6.5.2 Protocol VO56.07 Design Overview

#### Protocol VO56.07 Study Design

Phase:	Phase 1
Subject Population:	Adults ages 18 to 50 years (inclusive)
Randomization/Blinding:	RDBPC
Location of Study:	Austria
Number of Study Centers:	1

#### Protocol VO56.07 Duration of Study:

Total Study:	01 September 2007 to 10 March 2008
Screening:	Approximately 4 weeks
Treatment:	Approximately 4 months

Environmental Exposure Chambers (EEC) are sealed rooms in which subjects may be exposed to pollen at specific levels (measured in grains/m<sup>3</sup>) and clinical variables are measured during the exposure. EEC studies are done to eliminate the confounding variable different severity of pollen seasons from year to year. Since subjects do not take medication in the EEC, symptom scores alone are used to prove efficacy of therapy.

Protocol VO56.07 is described as a Phase I study in the BLA but the efficacy endpoints categorizes the study as Phase 2. Subjects enrolled had grass pollen-related ARC. The study consisted of an enrollment phase of one to six weeks. After screening, subjects underwent the first challenge in the EEC to determine whether or not they satisfy the screening criterion of an RTSS  $\geq 7$ .

Subjects who satisfied the EEC challenge criterion were randomized to study drug (ORALAIR 300 IR per day) or placebo group. Subjects began treatment and underwent a 2<sup>nd</sup> EEC challenge at Week 1, a 3<sup>rd</sup> challenge at Month 1, a 4<sup>th</sup> challenge at Month 2, and a 5<sup>th</sup> challenge at Month 4 (this is Visit 7). Visit 8 is the last of the study, and occurred 1-3 weeks after Visit 7.

The allergen exposure was to last two hours for the qualification session at baseline and four hours for the subsequent sessions. During each challenge, symptom data were recorded every 15 minutes; nasal airflow and nasal secretion weight every 30 minutes and FEV1 every hour.

These studies were performed in the Vienna Challenge Chamber is a specially designed sealed room in which a precisely defined concentration of allergen can be distributed and held constant. A standard grass pollen mix containing equal parts of *Dactylis glomerata*, *Poa pratensis*, *Lolium perenne* and *Phleum pratense* was used. The duration of the initial EEC sessions was 2 hour, and each challenge was 4 hours.

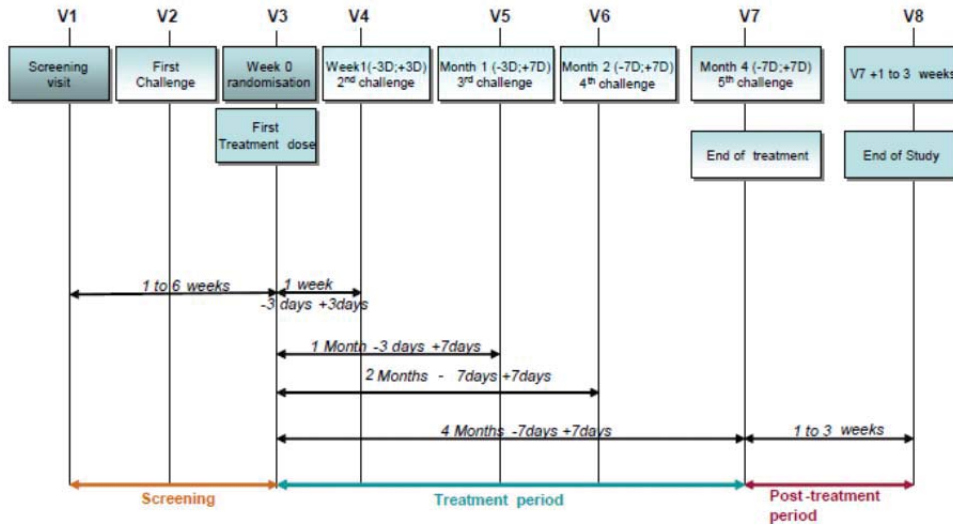
Subjects recorded the severity of nasal (sneezing, rhinorrhea, nasal pruritus and nasal congestion) and ocular symptoms (ocular pruritus and watery eyes) by direct input on a touch screen on a scale of 0 (absent) to 3 (severe) every 15 minutes during each allergen challenge in the EEC. FEV1 measurements were performed every 60 minutes during each EEC allergen challenge. Nasal airflow was measured by Active Anterior Rhinomanometry approximately every 30 min during each allergen challenge.

The study was conducted after the 2007 grass pollen season and prior to the 2008 grass pollen season, *i.e.* between the two grass pollen seasons.



**Figure 14. Design of Protocol VO56.07**

from original BLA 125471/000; Clinical Study Report VO56.07, p.48



6.5.3 Protocol VO56.07 Population

Inclusion:

Adults, 18-50 years of age  
Seasonal grass pollen-related ARC  $\geq 2$  pollen seasons  
+SPT (geometric wheal diameter  $> 3$  mm) to the 5 grass pollen allergen extract  
Specific IgE positive to grass pollen ( $>$ Class 2)  
RRTSS score  $\geq 12$   
Subjects who have a positive response to the baseline challenge test RTSS reaches seven at one time point at least during baseline challenge).

Exclusion:

Sensitization to pollens (other than the five grass pollens in ORALAIR) which are airborne during grass pollen season  
ARC due to perennial allergens  
Asthma that requires treatment other than beta-2 inhaled agonists.

6.5.4 Protocol VO56.07 Study Treatments or Agents Mandated by the Protocol

The formulation of study drug and placebo tablets is identical to previous studies. The batch number for the study drug was P0123, which was manufactured on April 27, 2006, and expired in March, 2008. The batch number for placebo was P0131, which was manufactured on May 6, 2006, and expired in May, 2008.

6.5.5 Protocol VO56.07 Directions for Use

Subjects were instructed to leave the tablet(s) under the tongue until complete dissolution before swallowing.

#### 6.5.6 Sites and Centers

This study was conducted in one center in Vienna, Austria. The Investigator was Professor Friedrich Horak. Stallergenes S.A. sponsored and managed this study. The protocol was written by Stallergenes S. A. (b)(4) was the Clinical Research Organization (CRO) commissioned for the data management, data analysis and clinical study report writing of this study.

#### 6.5.7 Protocol VO56.07 Surveillance/Monitoring

The safety of the investigational product was evaluated by monitoring AE through the use of daily diary cards (passive) and history/physical examinations (active) during the study visits. All subjects were seen within three weeks of the end of the ECC challenges.

Monitoring was performed by (b)(4), and included periodic visits for source data verification and to check compliance with the protocol, GCP and applicable regulatory requirements. Before being sent to the data management team of (b)(4), the CRFs were completed by the Investigator and checked by the monitor for accuracy, completeness and consistency. The CRF forms for active surveillance were included in the IND and BLA submissions, and were appropriate. Table 37 shows the schedule of study visits and monitoring.

**Table 30. Schedule of study visits and monitoring, Protocol VO56.07**  
from Original BLA 125471/000; Clinical Study Report VO56.07, p.55

Assessments	Screening V1 Within 6 weeks prior to V3	Screening V2 Any time between V1 and V3	Treatment period V3 Week 0 Randomi- sation	Treatment period V4 Week 1 (-3D;+3D)	Treatment period V5 Month 1 (-3D; +7D)	Treatment period V6 Month 2 (-7D; +7D)	Treatment period V7 Month 4 (-7D; +7D)	Follow-up Discharge V8 V7 + 1 to 3 weeks
Written Informed Consent	X							
Demographic data	X							
Medical/surgical history	X							
Habits and lifestyle	X							
Physical examination (including vital signs <sup>(1)</sup> )	X	X	X	X	X	X	X	X
Urinary pregnancy test <sup>(2)</sup> —all females	X		X		X	X	X	
Skin prick test	X				X	X	X	
Safety Laboratory parameters	X							X
Grass pollen specific IgE dosage	X							
Verification of inclusion/exclusion criteria	X	X	X					
Immunological markers: blood sample, saliva collection and nasal lavage			X			X	X	
Allergen challenge		X		X	X	X	X	
Randomisation			X					
Recording medications and procedures	X	X	X	X	X	X	X	X
Recording Adverse Events		X	X	X	X	X	X	X
Drug Dispensing and Return			X <sup>(3)</sup>			X	X	

(1) Vital signs: Supine, after 5 minutes' rest, blood pressure (BP) and pulse rate.

(2) Every month; one additional test was performed between Visit 6 and Visit 7. (3) Subject observation for 30 minutes after the first intake.

### 6.5.8 Protocol VO56.07 Endpoints and Criteria for Study Success

#### Primary efficacy assessment:

The average rhinoconjunctivitis total symptom score (ARTSS) [0-4] hours during the allergen challenge at endpoint (after four months of treatment or, in case of withdrawal, during the last available challenge). The rhinoconjunctivitis total symptom score (RTSS) was the sum of the six individual symptoms (sneezing, rhinorrhea, nasal pruritus, nasal congestion, ocular pruritus and watery eyes) as evaluated by the subject, using a score from 0 to 3:

0 = Symptoms are absent (no sign/symptom evident).

1 = Mild symptoms (sign/symptom clearly present/minimal awareness, easily tolerated).

2 = Moderate symptoms (definite awareness of sign/symptom, bothersome but tolerable).

3 = Severe symptoms (sign/symptom that is hard to tolerate; causes interference with activities of daily living).

The ARTSS [0-4] hours was calculated as the mean of the RTSS at all time points (16 time points, from 15 minutes to four hours) during the allergen exposure at endpoint. The ARTSS [0-4] hours can range between 0 and 18. The primary efficacy endpoint will be met if the decrease in ARTSS in the study drug group compared to the placebo group is  $\geq 30\%$  or a minimum difference in ARTSS of 1.2.

Secondary efficacy assessments:

- The change from baseline in ARTSS [0-2] hours during the allergen challenge at endpoint.
- The ARTSS [0-4] hours during the allergen challenge after one week and one, two and four months of treatment in order to define the onset of action.

*Reviewer's comment: the study was well designed to meet its primary endpoint.*

#### 6.5.9 Protocol VO56.07 Statistical Considerations & Statistical Analysis Plan

The null hypothesis is no difference between treatment (300 IR) and Placebo groups in the RTSS after 4 months of pretreatment.

No previous study in an allergen exposition chamber concerning grass pollen allergen extract SLIT was available. Consequently, the sample size was based on the following hypotheses:

- From a previous Phase II study performed by Stallergenes (VO34.04), ARTSS under placebo during the worst period of the grass pollen season was equal to five. Symptom scores in an allergen exposition chamber were expected to be more severe than in standard outdoor studies. Therefore an ARTSS of eight under placebo was retained, knowing that ARTSS can range from 0 to 18.
- Variability is lower in an allergen exposition chamber than in traditional studies. From previous studies performed in an allergen exposition chamber (whatever the study treatment), the coefficient of variation was often close to 50%, *i.e.* a standard deviation equal to half the mean.
- Efficacy of active treatment was expected to be 30% better than a placebo effect with an improvement in ARTSS of at least 1.2.

A sample size of 34 subjects per treatment group would have a power of 81% to detect a difference in ARTSS (mean of the sums of the six individual symptom scores at each time point during the allergen exposure) of 2.4 between active and placebo (mean score under placebo = 8; mean score under active treatment = 5.6, *i.e.* an improvement of 30%), assuming an overall alpha of 0.05 and a common standard deviation of 3.4.

Assuming a 20% screening failure rate and a 15% drop-out rate, 100 subjects had to be screened in order to have 40 randomized subjects in each group at the start of the study, and 34 at the endpoint.

## 6.5.10 Protocol VO56.07 Study Population and Disposition

### 6.5.10.1 Protocol VO56.07 Populations Enrolled/Analyzed

The Intention-To-Treat (ITT) population included all randomized subjects who received at least one dose of the investigational products (first dose taken during Visit 3). The ITT population was primary for efficacy analyses.

The Per Protocol (PP) Population was a subset of the ITT population and included all subjects who completed the study according to the protocol and had no major protocol violations.

Protocol violations were defined as major if they had an influence on the efficacy criteria.

For evaluation of the statistical plan to analyze efficacy, see the statistician's review.

#### 6.5.10.1.1 Protocol VO56.07 Demographics

There were no significant differences between the study drug and placebo groups in the safety, ITT, or PP group among the following variables: gender, age, weight, height, or BMI.

#### 6.5.10.1.2 Protocol VO56.07 Medical/Behavioral Characterization of the Enrolled Population

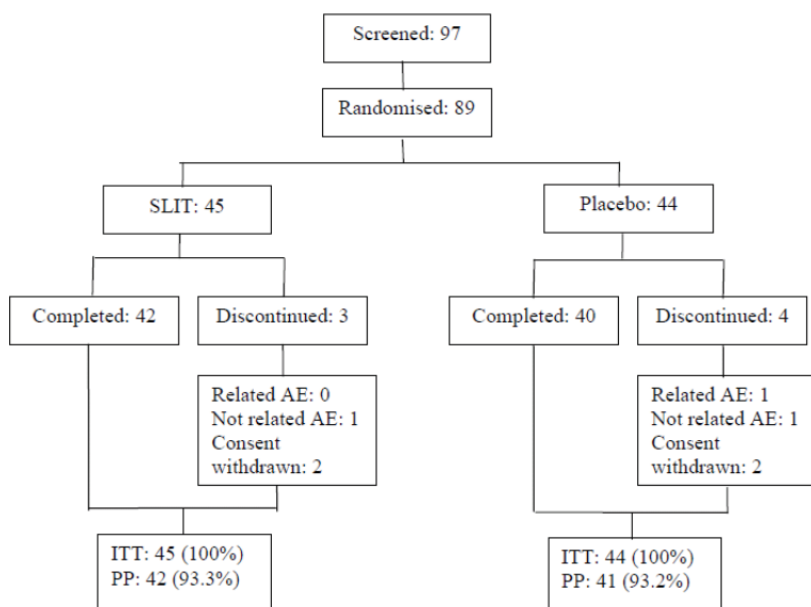
For this short term study EEC, there are no applicable cofactors in the study population.

#### 6.5.10.1.3 Protocol VO56.07 Subject Disposition

### Figure 15. Subject disposition in Protocol VO56.07

from Original BLA 125471/000; Clinical Study Report VO56.07, p.78

Figure 10.1.1- 1: Overall Subject Disposition



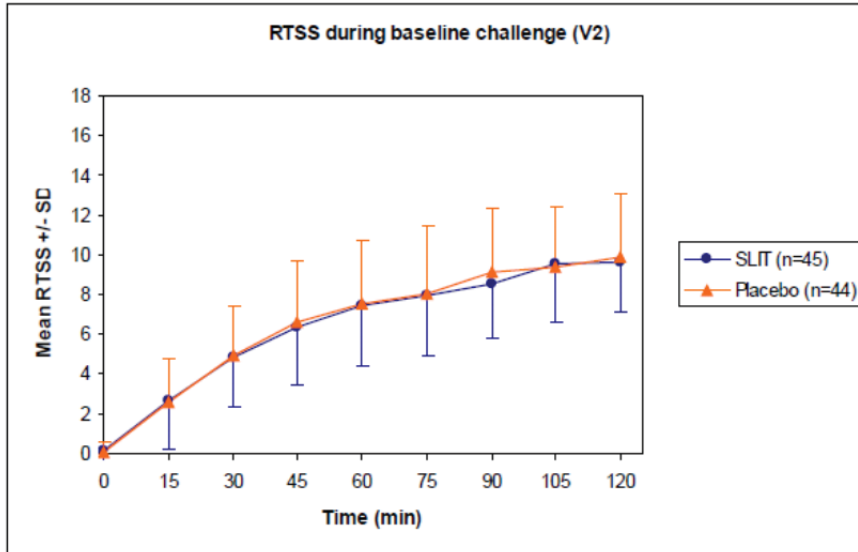
6.5.11 Protocol VO56.07 Efficacy Analyses

**6.5.11.1 Protocol VO56.07 Analyses of Primary Endpoint(s)**

The primary efficacy variable is the difference in the RTSS between the study drug and placebo groups after 4 months of treatment. The first necessary assessment is whether the two study groups were equally affected at baseline by the EEC exposure. The figure below demonstrates that the two groups responded equally during the initial challenge, with a mean RTSS of 8 after 2 hours of exposure.

**Figure 16. RTSS during baseline ECC challenge in Protocol VO56.07**

Adapted from Original BLA 125471/000; Clinical Study Report VO56.07, p.88



After 4 months of treatment, the ARTSS was decreased by 1.96, or a 28.7% in the 300 IR ORALAIR group with acceptable 95% CI (95% CI 13.7%; 58.3%).

**Table 31. ARTSS in ECC after ORALAIR therapy**

from original BLA 125471/000; Clinical Study Report VO56.07, p.89

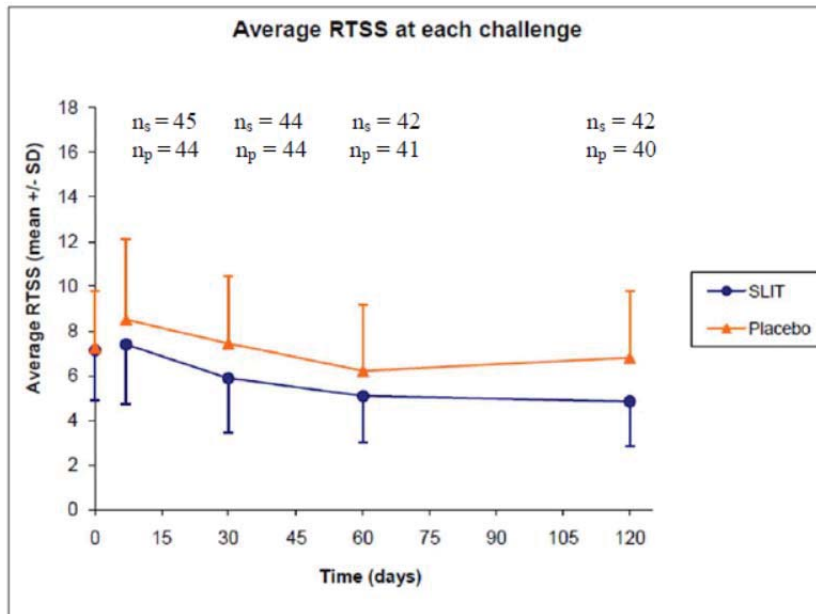
Difference vs. Placebo in ARTSS [0-4] hours [95% CI] (p-value) (a)	ARTSS [0-4] hours at endpoint Adjusted Mean (SE)	ARTSS [0-4] hours at endpoint Adjusted Mean (SE)
	SLIT(N=45)	Placebo (N=44)
-1.97 [-2.99 ; -0.94] (0.0003*)	4.88 (0.363)	6.84 (0.367)

**6.5.11.2 Protocol VO56.07 Analyses of Secondary Endpoints**

Analysis of secondary endpoints demonstrates that after one month of treatment, that the ARTSS of the 300 IR treatment group was decreased from baseline after 2 hours of exposure. These differences remained and increased throughout the duration of treatment.

**Figure 17. Average RTSS at each ECC challenge, Protocol VO56.07**

Adapted from original BLA 125471/000; Clinical Study Report VO56.07, p.97



### 6.5.11.3 Protocol VO56.07 Subpopulation Analyses

There were no subpopulations to be analyzed.

### 6.5.11.4 Protocol VO56.07 Dropouts and/or Discontinuations

from sBLA 125471/000; Clinical Study Report VO56.07, p.115

“There were no missing data during the allergen challenges except a nasal secretion weight at one time point and for one subject. In case of dropouts, the last available outcome was used as endpoint (Last Observation Carried Forward method - LOCF).”

### 6.5.11.5 Protocol VO56.07 Exploratory and Post Hoc Analyses

There was no difference in skin prick testing (SPT) between the study drug and placebo groups after 4 months of treatment. These data may be found in original BLA 125471/000; Clinical Study Report VO56.07, p.113.

Levels of “5-grasses” Specific IgE rose by ~2.5 fold in the study drug group but not placebo group. These data may be found in original BLA 125471/000; Clinical Study Report VO56.07, p.2756.

### 6.5.12 Protocol VO56.07 Safety Analyses

#### 6.5.12.1 Protocol VO56.07 Methods

Safety was monitored during visits by history and physical exams, and clinical laboratory exams including urine pregnancy tests as shown on the study plan. Subjects kept diary cards to record AE between study visits.

### 6.5.12.2 Protocol VO56.07 Overview of Adverse Events

There were more drug-related AE in the treatment group, and more AE that led to study withdrawal in the treatment group. There were no SAE or deaths. Most of the TEAE in the subjects in the treatment group that were considered related to the study drug were consistent with application site reactions (e.g. tongue, lips) and were Grade 1 or 2 (mild or moderate severity that did not require discontinuation of therapy).

**Table 32. Incidence of TEAE in Protocol VO56.07**

from sBLA 125471/000; Clinical Study Report VO56.07, p.123

	SLIT (N = 45) n (%)	Placebo (N = 44) n (%)
Total number of pre-treatment AEs	0	1
Subjects with at least one pre-treatment AE	0	1 (2.3)
Total number of TEAEs	73	39
Subjects with at least one TEAE	27 (60.0)	14 (31.8)
Subjects withdrawn due to a TEAE	1 (2.2)	2 (4.5)
Subjects with at least one treatment-related* TEAE	23 (51.1)	2 (4.5)
Subjects with at least one severe TEAE	0	0
Subjects with at least one serious TEAE (SAE)	0	0
Subjects with at least one treatment-related* SAE	0	0
Number of deaths	0	0

**Table 33. TEAE occurring in at least 5% of subjects in Protocol VO56.07**

From sBLA 125471/000; Clinical Study Report VO56.07, p.124

System Organ Class Preferred Term	SLIT (N=45) nAE	SLIT (N=45) n	SLIT (N=45) %	Placebo (N=44) nAE	Placebo (N=44) n	Placebo (N=44) %
Number of subjects with at least one TEAE*	73	27	60.0	39	14	31.8
Ear and labyrinth disorders						
Ear pruritus	3	3	6.7	0	0	0
Gastrointestinal disorders						
Oral pruritus	21	16	35.6	0	0	0
Infections and infestations						
Nasopharyngitis	2	2	4.4	5	4	9.1
Nervous system disorders						
Headache	17	8	17.8	14	8	18.2
Respiratory, thoracic and mediastinal disorders						
Throat irritation	19	16	35.6	0	0	0

nAE = number of adverse events, n = number of subjects with a TEAE, % = percentage of subjects

### 6.5.12.3 Protocol VO56.07 Deaths

There were no deaths.

### 6.5.12.4 Protocol VO56.07 Nonfatal Serious Adverse Events

There were no severe AE or SAE.



#### **6.5.12.5 Protocol VO56.07 Adverse Events of Special Interest (AESI)**

None

#### **6.5.12.6 Protocol VO56.07 Clinical Test Results**

There were no significant abnormalities in clinical laboratory tests or vital signs in this study.

#### **6.5.12.7 Protocol VO56.07 Dropouts and/or Discontinuations**

There were three dropouts due to AE.

Subject (b) (ORALAIR Study Drug group) had wisdom tooth surgery on 14 Oct 2007 and two days later presented with moderate oral inflammation. The subject received an antibiotic from her dentist and the AE resolved.

Subject (b) was in the Placebo group and presented with a moderate headache on 13 Dec 2007. This was the second headache the subject experienced during the trial. The investigational drug was discontinued on 19 December 2007 and the headache resolved. The event was considered probably related to the investigational product.

On 21 November 2007, Subject (b) presented with moderate pneumonia. The investigator considered the event not related to the investigational product but administration of the investigational product was definitively discontinued on 07 December 2007. The event resolved by 18 December 2007. The subject was withdrawn from the study on 18 December 2007.

*It is of the reviewer's opinion that these AE are not due to the study drug.*

#### **6.5.13 Protocol VO56.07 Reviewer's conclusions:**

In Protocol VO56.07 subjects who were treated with ORALAIR for four months had an ARTSS that was 28.7% lower than the placebo group CI (95% CI 13.7%; 58.3%). This decrease does not meet the proposed decrease of 30%, the difference in ARTSS was 1.96, which was above the proposed minimum difference of 1.2. AE were mild or moderate, and there were no SAE.

### **6.6 Trial #6 (Pivotal for safety and efficacy)**

*Protocol VO61.08USA: A randomized, double-blind, placebo-controlled, multi-center, phase III study of the efficacy and safety of 300 IR sublingual immunotherapy (SLIT) administered as allergen-based tablets once daily to adult subjects suffering from grass pollen rhinoconjunctivitis.*

#### **6.6.1 Protocol VO61.08USA Objectives (Primary, Secondary, etc)**

Primary Objective: To assess the efficacy of sublingual tablets of grass pollen allergen extract during the pollen period on the daily Combined Score (CS), which takes into account the Rhinoconjunctivitis Total Symptom Score (RTSS) and the Rescue Medication Score (RMS).

Secondary Objectives (critical to evaluation of the BLA): To assess the efficacy of sublingual tablets of grass pollen allergen extract on:

1. The daily CS on the non-primary analysis set and/or other evaluation periods.
2. The daily Adjusted Symptom Score (ASS): A score taking into account the daily RTSS and daily rescue medication use. - The daily RTSS of the six rhinoconjunctivitis symptoms sneezing, rhinorrhea, nasal pruritus, nasal congestion, ocular pruritus and watery eyes.
3. The daily RMS.

#### 6.6.2 Protocol VO61.08USA Design Overview

##### Protocol VO61.08 Study Design

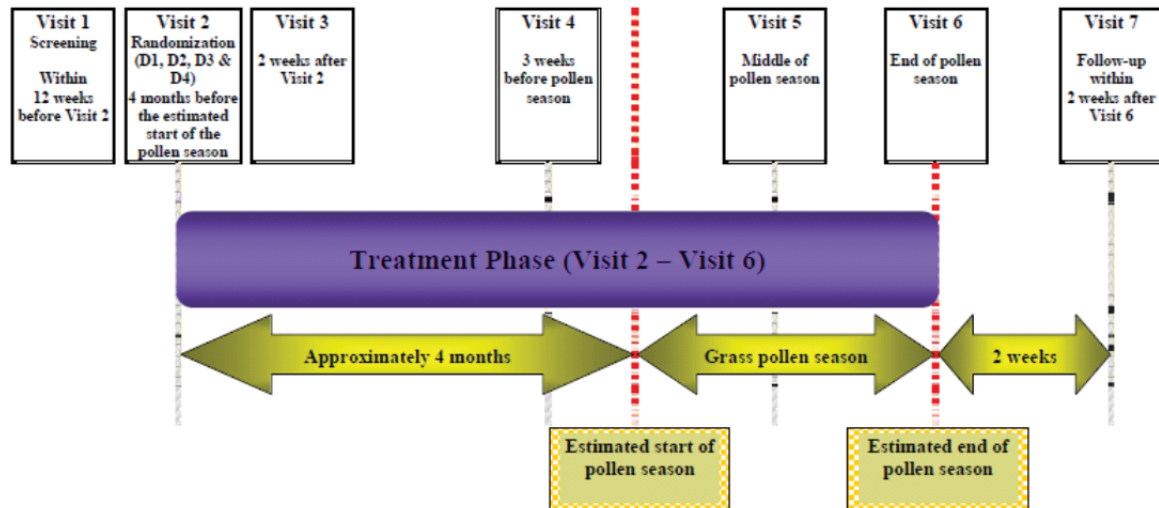
Phase: Phase 3  
Subject Population: Adults ages 18 to 65 years (inclusive)  
Randomization/Blinding: RDBPC  
Location of Study: United States  
Number of Study Centers: 51

##### Protocol VO61.08 Duration of Study:

Total Study: 15 December 2008 to 13 August 2009  
Screening: 1-12 weeks  
Treatment: Approximately 6 months  
Follow-up: 2 weeks

#### **Figure 18. Study Design of Protocol VO61.08**

from original BLA 125471/000; Clinical Study Report VO61.08, p.27



### 6.6.3 Protocol VO61.08USA Population

- Inclusion:** Adults, 18-50 years of age  
Seasonal grass pollen-related ARC  $\geq 2$  pollen seasons  
+SPT (geometric wheal diameter  $> 5$  mm) to Timothy grass extract  
Specific IgE positive to grass pollen ( $>$ Class 2)  
RRTSS score  $\geq 12$
- Exclusion:** Sensitization to pollens (other than the five grass pollens in ORALAIR) which are airborne during grass pollen season ARC due to perennial allergens  
Asthma that requires treatment other than beta-2 inhaled agonists.

### 6.6.4 Protocol VO61.08USA Study Treatments or Agents Mandated by the Protocol

The formulation of study drug and placebo tablets is identical to previous studies. The batch number for the study drug and placebo was P0261 and P0276, respectively. They were both manufactured in June 2008, and both expired in June, 2010.

### 6.6.5 Protocol VO61.08USA Directions for Use

Subjects were instructed to leave the tablet(s) under the tongue until complete dissolution before swallowing.

### 6.6.6 Protocol VO61.08USA Sites and Centers

This study was conducted at 51 study centers in the United States of America (USA) and subjects were managed as outpatients. The Medical Director of the study was Olivier de Beaumont of Stallergenes. The Coordinating Investigator was Linda S. Cox.

### 6.6.7 Protocol VO61.08USA Surveillance/Monitoring

The safety of the investigational product was evaluated by monitoring AE through the use of daily diary cards (passive) and history/physical examinations (active) during the study visits. Each study visit was conducted according to the CSR, which was appropriate for safety surveillance.

**Table 34. Schedule of study visits and subject monitoring in Protocol VO61.08.**

from original BLA 125471/000; Clinical Study Report VO61.08 p40

Study assessments	Visit 1 (Screening) <i>Within 12 weeks before Visit 2</i> )	Visit 2 (4 months before the pollen season starts) <b>Day 1</b>	Visit 2 (4 months before the pollen season starts) <b>Day 2</b>	Visit 2 (4 months before the pollen season starts) <b>Day 3</b>	Visit 2 (4 months before the pollen season starts) <b>Day 4</b>	Visit 3 (2 weeks after Visit 2)	Visit 4 (3 weeks before the pollen season starts)	Visit 5 (Middle of pollen season)	Visit 6 End of Treatment Visit (End of the pollen season)	Visit 7 Follow-up Visit (Within 2 weeks after Visit 6)
Written consent	X									
Sign EpiPen® training form		X								
Inclusion and exclusion criteria	X									
Eligibility of patient	X									
Medical and allergy history	X									
Demographics	X								X	
Asthma history and evaluation	X								X	
FEV <sub>1</sub>	X									
12-Lead electrocardiogram (all patients 50 years and older)	X									
Physical examination	X	X				X	X	X	X	X
Vital signs	X	X	X			X	X	X	X	X
RRSS	X									
Safety laboratory tests	X									
Pregnancy test (urine) – all females of child-bearing potential	X	X				X	X	X	X	X
Immunological markers (IgE and IgG <sub>4</sub> )	X							X	X	
SPT	X								X	
Concomitant medication	X	X	X			X	X	X	X	X
Adverse events	X	X	X			X	X	X	X	X
Randomization	X									
Administration of investigational product in the clinic	X	X	X							
Phone call										X

Study assessments	Visit 1 (Screening) Within 12 weeks before Visit 2)	Visit 2 (4 months before the pollen season starts) Day 1	Visit 2 (4 months before the pollen season starts) Day 2	Visit 2 (4 months before the pollen season starts) Day 3	Visit 2 (4 months before the pollen season starts) Day 4	Visit 3 (2 weeks after Visit 2)	Visit 4 (3 weeks before the pollen season starts)	Visit 5 (Middle of pollen season)	Visit 6 End of Treatment Visit (End of the pollen season)	Visit 7 Follow-up Visit (Within 2 weeks after Visit 6)
Investigational products dispensed/checked/returned		X				X	X		X	
EpiPen® (2-pack) dispensed	X					X**	X**	X**		
Daily record card issued/checked/returned						X	X	X	X	X
Rescue medication dispensed/checked/returned							X	X	X	X
RQLQ		X								
Global evaluation										
Economic evaluation									X	X

FEV<sub>1</sub>: Forced expiratory volume in 1 second, GINA: Global Initiative for Asthma, Ig: Immunoglobulin, RQLQ: Rhinoconjunctivitis Quality of Life Questionnaire, RRTSS: Retrospective Rhinoconjunctivitis Total Symptom Score, SPT: Skin prick test.

Patients who withdrew during the Treatment Phase had to complete the assessments performed at Visit 6 (Early Termination Visit).

\* At phone call.

\*\* If previous EpiPen® dispensed had been used for an AE which did not require the patient's withdrawal from the study (see [Section 9.3.3](#)).

**Notes:**

**Screening Phase (1 to 12 weeks):** Patients were screened for eligibility. Written informed consent was obtained.

**Treatment Phase (approximately 6 months):** Visit 2 (Day 1) through Visit 6 comprised the Treatment Phase.

**Follow-up Phase (2 weeks):** This visit was to be within 2 weeks after Visit 6.

The Contract Research Organization contracted by Stallergenes to manage this study was (b)(4) Protocol writing, CRF development, data management, statistical analysis and writing of initial drafts of the CSR were performed by (b)(4) on behalf of Stallergenes. Study monitoring and medical monitoring was performed by (b)(4)

#### 6.6.8 Protocol VO61.08USA Endpoints and Criteria for Study Success

The primary efficacy variable is the daily CS, a daily subject-specific score taking into account the subject's daily RTSS and RMS, assuming equivalent importance of symptoms and medication scores. The CS is calculated as:  $CS = (RTSS / 6 + RMS) / 2$ .

Secondary efficacy variables of significance are the two variables that comprise the CS, the RTSS and the RMS. The daily RTSS is the sum of the six (non-missing) rhinoconjunctivitis symptom scores as evaluated by the subject using a score from 0 to 3. The daily RMS is assigned daily to the different medications used as rescue medication. The primary endpoint will have been successfully met if the CS of the ORALAIR study drug group is decreased by  $\geq 15\%$  compared to the placebo group with a lower limit of the 95% CI  $\geq 10\%$ .

#### 6.6.9 Protocol VO61.08USA Statistical Considerations & Statistical Analysis Plan

The null hypothesis is no difference between treatment (300 IR) and Placebo groups in the RTSS after 4 months of pretreatment.

No previous study in an allergen exposition chamber concerning grass pollen allergen extract SLIT was available. Consequently, the sample size was based on the following hypotheses:

- From a previous Phase II study performed by Stallergenes (VO34.04), ARTSS under placebo during the worst period of the grass pollen season was equal to five. Symptom scores in an allergen exposition chamber were expected to be more severe than in standard outdoor studies. Therefore an ARTSS of eight under placebo was retained, knowing that ARTSS can range from 0 to 18.
- Variability is lower in an allergen exposition chamber than in traditional studies. From previous studies performed in an allergen exposition chamber (whatever the study treatment), the coefficient of variation was often close to 50%, *i.e.* a standard deviation equal to half the mean.
- Efficacy of active treatment was expected to be 30% better than a placebo effect with an improvement in ARTSS of at least 1.2.

A sample size of 34 subjects per treatment group would have a power of 81% to detect a difference in ARTSS (mean of the sums of the six individual symptom scores at each time point during the allergen exposure) of 2.4 between active and placebo (mean score under placebo = 8; mean score under active treatment = 5.6, *i.e.* an improvement of 30%), assuming an overall alpha of 0.05 and a common standard deviation of 3.4.

Assuming a 20% screening failure rate and a 15% drop-out rate, 100 subjects had to be screened in order to have 40 randomized subjects in each group at the start of the study, and 34 at the endpoint.

6.6.10 Protocol VO61.08USA Study Population and Disposition

**6.6.10.1 Protocol VO61.08USA Populations Enrolled/Analyzed**

The Safety Set consisted of the 473 randomized subjects (233 in the 300 IR group and 240 in the Placebo group) who received at least one dose of the investigational product.

The FAS consisted of the 438 subjects (210 in the 300 IR group and 228 in the Placebo group) from the Safety Set who had at least one Combined Score (CS) while on treatment during the pollen period.

The PP set consisted of the 416 subjects (204 in the 300 IR group and 212 in the Placebo group) from the FAS who had at least 14 valid CS days during the pollen period while on treatment and who completed the study according to the protocol.

The FAS is the same as the ITT set except for 35 subjects who were excluded from the FAS due to not having at least one CS during the pollen period while on treatment. Also 30 subjects withdrew before the start of the pollen season.

**Table 35. Populations enrolled/analyzed for Protocol VO61.08USA**

from sBLA 125471/000; Clinical Study Report VO61.08 p84

Description	Treatment Group Placebo (N = 240)	Treatment Group Placebo (N = 240)	Treatment Group 300 IR (N = 233)	Treatment Group 300 IR (N = 233)	Treatment Group Total (N = 473)	Treatment Group Total (N = 473)
	n	%	n	%	n	%
Patients randomized	240	100.0	233	100.0	473	100.0
Patients in the Safety Set	240	100.0	233	100.0	473	100.0
Patients in the FAS	228	95.0	210	90.1	438	92.6
Patients in the PPS	212	88.3	204	87.6	416	87.9

*6.6.10.1.1 Protocol VO61.08USA Demographics*

Age, race, BMI and ethnicity are equally distributed among each of the study groups. Also equally distributed are duration of ARC and the presence of asthma.

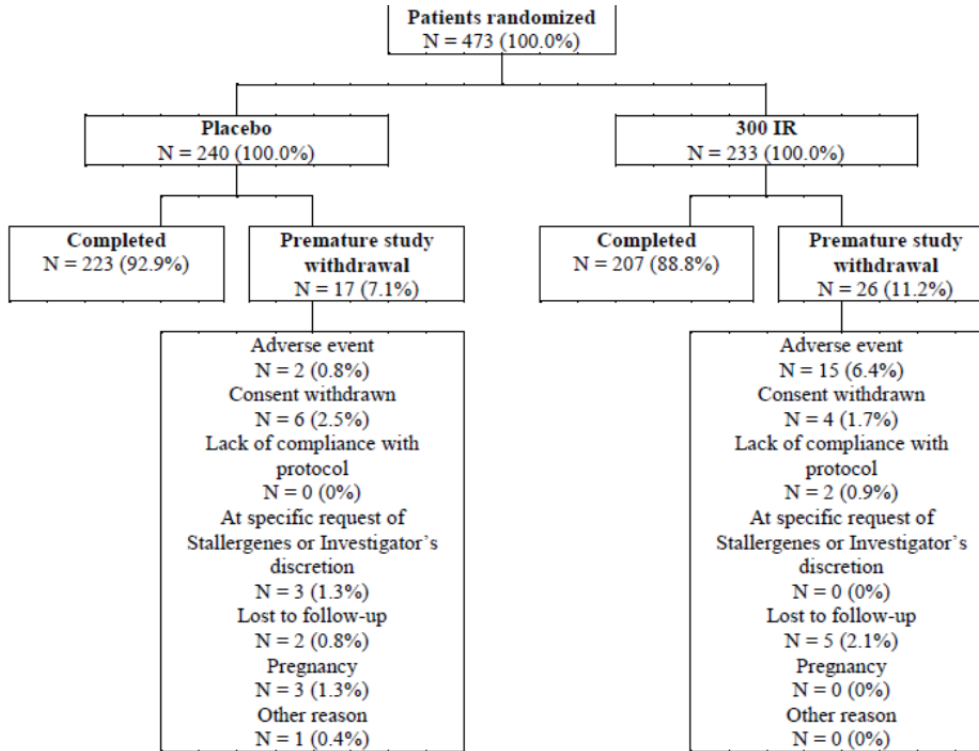
*6.6.10.1.2 Protocol VO61.08USA Medical/Behavioral Characterization of the Enrolled Population*

See section 6.6.11.3, which discusses the distribution of subjects with asthma, the medical characteristic of interest.

6.6.10.1.3 Protocol VO61.08USA Subject Disposition

**Figure 19. Subject disposition in Protocol VO61.08USA**

from original BLA 125471/000; Clinical Study Report VO61.08 p81



6.6.11 Protocol VO61.08USA Efficacy Analyses

**6.6.11.1 Protocol VO61.08USA Analyses of Primary Endpoint(s)**

The primary efficacy endpoint is the daily CS during the pollen period while on treatment with the primary analysis done for the FAS. As shown below, this primary endpoint point estimate was met, with a decrease in CS of 28.2% in the study drug compared to the placebo group. The lower 95% CI is 12.9%.

**Table 36. Primary efficacy analysis of daily CS, Protocol VO61.08USA**

from original BLA 125471/000; Clinical Study Report VO61.08 p95

Tx	N	Mean	Point Estimate	95% CI	P value	Relative LS mean difference (%)
300 IR	208	0.32	-.126	-0.194, -0.058	0.0003	-28.2
Placebo	228	0.45				

**6.6.11.2 Protocol VO61.08USA Analyses of Secondary Endpoints**

Secondary endpoints that contribute to the determination of efficacy are those that contribute to the CS, which is an average of the Rhinoconjunctivitis Total Symptom Score (RTSS) and the Rescue Medication Score (RMS).



The RTSS is a sum of six RC symptoms (sneezing, rhinorrhea, nasal pruritus, nasal congestion, ocular pruritus and watery eyes), each scored daily by the subject using a 4-point scale from 0 to 3 where 0 = absent and 3 = severe symptoms. Analysis of the FAS demonstrates that RTSS significantly differed between the two groups.

**Table 37. AASS in Protocol VO61.08USA**

from original BLA 125471/000; Clinical Study Report VO61.08 p102

<b>Tx</b>	<b>N</b>	<b>Mean</b>	<b>Point Estimate</b>	<b>95% CI</b>	<b>P value</b>	<b>Relative LS mean difference (%)</b>
300 IR	208	3.98	-1.239	-1.94, -0.53	0.0006	-23.7
Placebo	228	5.22				

The RMS is a score of medications taken for relief of ARC symptoms. Analysis of the FAS demonstrates the RMS was decreased in the ORALAIR 300 IR study drug group compared to the placebo group.

**Table 38. RMS in Protocol VO61.08USA**

from original BLA 125471/000; Clinical Study Report VO61.08 p104

<b>Tx</b>	<b>N</b>	<b>Mean</b>	<b>Point Estimate</b>	<b>95% CI</b>	<b>P value</b>	<b>Relative LS mean difference (%)</b>
300 IR	208	0.11	-0.092	-0.146 -0.038	0.0009	-46.5
Placebo	228	0.20				

#### 6.6.11.3 Protocol VO61.08USA Subpopulation Analyses

At Screening (Visit 1), 33 (15.7%) subjects in the 300 IR group and 48 (21.1%) subjects in the Placebo group had asthma. Of these, two subjects in the 300 IR group and one subject in the Placebo group had a diagnosis of asthma at Screening and no diagnosis of asthma at Endpoint. Of the subjects who did not have asthma at screening, two in the 300 IR group and four in the Placebo group did so at Endpoint.

*Reviewer's comment: There is no evidence from this study that the study drug alleviates or modifies the course of asthma, or induces asthma.*

**6.6.11.4 Protocol VO61.08USA Dropouts and/or Discontinuations**

from sBLA 125471/000; Clinical Study Report VO61.08 p71

“Some subjects could be excluded from the primary analysis due to a lack of daily CS data during the pollen period while on treatment, for example, subjects withdrawn before the start of the pollen period or subjects with missing daily record card data. These drop-outs were accounted for in the sample size calculations. However, if more than 5% of the subjects included in the Safety Set had no valid daily CS, an additional sensitivity analysis using the same ANCOVA model as the one specified for the ACS was to be performed on the ACS for the Safety Set, using the following imputation method: For subjects in the 300 IR group, the missing ACS values were replaced by the mean ACS of the Placebo group and for subjects in the Placebo group, the missing ACS values were replaced by the mean ACS of the 300 IR group. In addition, summary statistics of ACS (based on the imputation method) are provided for the pollen period on the Safety Set by treatment group.”

*Reviewer’s comment: The statistical reviewer agreed with this plan for handling of dropouts and/or discontinuations*

**6.6.11.5 Protocol VO61.08USA Exploratory and Post Hoc Analyses**

There were no differences between the study drug and the placebo groups in grass-specific serum IgG4 and IgE at the end of the pollen season.

**6.6.12 Protocol VO61.08USA Safety Analyses**

**6.6.12.1 Protocol VO61.08USA Methods**

As with all these allergy immunotherapy efficacy studies, AE were monitored with diary record cards and during investigational study visits.

**6.6.12.2 Protocol VO61.08USA Overview of Adverse Events**

The overview below demonstrates a greater incidence of TEAE among the study drug group. There were no serious TEAE in either the study drug or placebo group, and fewer SAE in the study drug group.

**Table 39. Incidence of TEAE in Protocol VO61.08USA**

from original BLA 125471/000; Clinical Study Report VO61.08 p129

**Treatment group**

Description	Placebo	Placebo	300 IR	300 IR
	(N = 240) n	(N = 240) %	(N = 233) n	(N = 233) %
Number of patients with: At least one TEAE	184	76.7	191	82.0
At least one SAE	4	1.7	2	0.9
At least one serious TEAE	2	0.8	2	0.9
At least one drug-related TEAE	54	22.5	128	54.9
At least one serious drug-related TEAE	0	0.0	0	0.0
An AE leading to premature study withdrawal	2	0.8	15	6.4
An AE leading to death	0	0.0	0	0.0

TEAE were generally mild or moderate in severity, and limited to areas of local exposure to the drug. Those that occurred in greater than 5% of the subjects and differed in incidence between the Placebo and 300 IR study drug group are shown in Table 48.

**Table 40. TEAE that occurred in > 5% of subjects, Protocol VO61.08**

from original BLA 125471/000; Clinical Study Report VO61.08 p136

<b>System Organ Class Preferred term</b>	<b>Mild Rel (%)</b>	<b>Mild NR (%)</b>	<b>Moderate Rel (%)</b>	<b>Moderate NR (%)</b>	<b>Severe Rel (%)</b>	<b>Severe NR (%)</b>
<b>Patients with TEAEs*</b>	113 (48.5)	75 (32.2)	68 (29.2)	108 (46.4)	9 (3.9)	58 (24.9)
<b>Respiratory, thoracic and mediastinal disorders</b>	59 (25.3)	22 (9.4)	34 (14.6)	23 (9.9)	4 (1.7)	9 (3.9)
<b>Throat irritation</b>	44 (18.9)	0 (0.0)	28 (12.0)	1 (0.4)	3 (1.3)	0 (0.0)
<b>Oropharyngeal pain</b>	5 (2.1)	4 (1.7)	1 (0.4)	5 (2.1)	1 (0.4)	2 (0.9)
<b>Nasal Congestion</b>	4 (1.7)	6 (2.6)	1 (0.4)	4 (1.7)	1 (0.4)	3 (1.3)
<b>Cough</b>	3 (1.3)	4 (1.7)	1 (0.4)	5 (2.1)	0 (0.0)	2 (0.9)
<b>Pharyngeal oedema</b>	3 (1.3)	1 (0.4)	7 (3.0)	0 (0.0)	1 (0.4)	0 (0.0)
<b>Gastrointestinal disorders</b>	92 (39.5)	14 (6.0)	48 (20.6)	13 (5.6)	2 (0.9)	6 (2.6)
<b>Oral Pruritus</b>	45 (19.3)	0 (0.0)	19 (8.2)	0 (0.0)	0 (0.0)	0 (0.0)
<b>Oedema mouth</b>	15 (6.4)	0 (0.0)	10 (4.3)	0 (0.0)	1 (0.4)	0 (0.0)
<b>Paraesthesia oral</b>	22 (9.4)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
<b>Infections and infestations</b>	2 (0.9)	31 (13.3)	2 (0.9)	59 (25.3)	2 (0.9)	25 (10.7)
<b>Nasopharyngitis</b>	0 (0.0)	15 (6.4)	0 (0.0)	20 (8.6)	0 (0.0)	9 (3.9)
<b>Upper respiratory tract infection</b>	2 (0.9)	8 (3.4)	0 (0.0)	8 (3.4)	0 (0.0)	2 (0.9)
<b>Sinusitis</b>	0 (0.0)	1 (0.4)	0 (0.0)	7 (3.0)	0 (0.0)	6 (2.6)
<b>Nervous system disorders</b>	8 (3.4)	4 (1.7)	9 (3.9)	17 (7.3)	0 (0.0)	8 (3.4)
<b>Headache</b>	2 (0.9)	2 (0.9)	4 (1.7)	8 (3.4)	0 (0.0)	4 (1.7)
<b>Skin and subcutaneous tissue disorders</b>	14 (6.0)	6 (2.6)	10 (4.3)	7 (3.0)	0 (0.0)	1 (0.4)

System Organ Class Preferred term	Mild Rel (%)	Mild NR (%)	Moderate Rel (%)	Moderate NR (%)	Severe Rel (%)	Severe NR (%)
Ear and labyrinth disorders	25 (10.7)	4 (1.7)	14 (6.0)	0 (0.0)	1 (0.4)	1 (0.4)
Ear Pruritus	25 (10.7)	0 (0.0)	13 (5.6)	0 (0.0)	1 (0.4)	0 (0.0)
Eye disorders	6 (2.6)	5 (2.1)	9 (3.9)	7 (3.0)	0 (0.0)	4 (1.7)
Eye Pruritus	3 (1.3)	3 (1.3)	7 (3.0)	4 (1.7)	0 (0.0)	1 (0.4)
Injury, poisoning and procedural complications	1 (0.4)	4 (1.7)	0 (0.0)	12 (5.2)	0 (0.0)	9 (3.9)
Musculoskeletal and connective tissue disorders	0 (0.0)	3 (1.3)	0 (0.0)	11 (4.7)	0 (0.0)	7 (3.0)
General disorders and administration site conditions	2 (0.9)	2 (0.9)	6 (2.6)	5 (2.1)	0 (0.0)	2 (0.9)

#### 6.6.12.3 Protocol VO61.08USA Deaths

There were no deaths.

#### 6.6.12.4 Protocol VO61.08USA Nonfatal Serious Adverse Events

There were 4 SAE in the Placebo Group and 2 in the 300 IR study drug group.

**Table 41. SAE in Protocol VO61.08USA**

from sBLA 125471/000; Clinical Study Report VO61.08 p139

System Organ Class Preferred Term	Treatment group	Treatment group	Treatment group	Treatment group
	Placebo (N = 240) n	Placebo (N = 240) %	300 IR (N = 233) n	300 IR (N = 233) %
Patients with at least one SAE	4	1.7	2	0.9
<b>Gastrointestinal disorders</b>	2	0.8	1	0.4
Palatal disorder	0	0.0	1	0.4
Haematochezia	1	0.4	0	0.0
Intestinal obstruction	1	0.4	0	0.0
<b>Infections and infestations</b>	1	0.4	0	0.0
Gastroenteritis	1	0.4	0	0.0
Wound infection	1	0.4	0	0.0
<b>Neoplasms benign, malignant and unspecified</b>	0			
Neuroendocrine Carcinoma	0			
<b>Injury and poisoning</b>	0.4	0	0	0
Ankle fracture	0.4	0	0	0

The only SAE that is potentially related to the study drug was the “Palatal disorder.” This subject presented on Day 177 (six days past the last dose of study drug) with impaired palatal elevation of the left anterior faucial pillar. There were no other symptoms, and 19 days later the subject was examined by an otolaryngologist. Endoscopy showed that the subject was able to achieve normal, symmetrical palatal closure during appropriate voiced activities and the vocal folds bilaterally were assessed to be within functional normal limits. The investigator considered the event to be unlikely related to the study drug and was more likely related to a tonsillectomy performed in 2002.

*The reviewer agrees with the investigator’s assessment that this event is not due to study drug.*

**6.6.12.5 Protocol VO61.08USA Adverse Events of Special Interest (AESI)**

Subject 1038/08 is a 33 year old male who was hospitalized on Day 71 with a hepatic lesion that was ultimately diagnosed as a metastatic neuroendocrine neoplasm. The subject was withdrawn from the study on that same day, and the event is considered by the investigator to be not related to the study drug.

*The reviewer concurs with this assessment.*

**6.6.12.6 Clinical Test Results**

Laboratory values that varied significantly from the reference range (“panic values”) are shown below.

**Table 42. Abnormal laboratory values of interest in Protocol VO61.08USA**

from original BLA 125471/000; Clinical Study Report VO61.08 p143

Treatment Group Patient number	Visit	Test	Result	Unit	Reference range	
					Lower limit	Upper limit
300 IR 1001/24	Visit 6	Eosinophils (absolute)	0.92	x10 <sup>9</sup> /L	0	0.56
1003/15	Visit 6	Eosinophils (absolute)	1.52	x10 <sup>9</sup> /L	0	0.56
1026/20	Visit 6	Non-fasting glucose	1.9	mmol/L	3.6	7.7
1035/06	Early termination	Neutrophils (absolute)	0.76	x10 <sup>9</sup> /L	2.03	8.36
	Unscheduled	Neutrophils (absolute)	0.88	x10 <sup>9</sup> /L	2.03	8.36

The rise in eosinophils in two subjects is expected and of no concern in the context of their allergic status and the use of study drug.

Subject 1035/06 had pharyngeal edema after ingestion of study drug on January 21, 2009, during Visit 2. The low neutrophil count shown above was first measured on January 29, 2009, and repeated on February 12, 2009. In addition, one subject was found to have a low non-fasting glucose.

*Reviewer's comment: Neither the low glucose nor the neutropenia are considered by the reviewer to be related to the study drug.*

#### **6.6.12.7 Dropouts and/or Discontinuations**

A total of 43 subjects prematurely withdrew from the study; 17 (7.1%) from the placebo group and 26 (11.2%) from the study drug group. Two of the dropouts in the placebo group and 15 subjects in the study drug group withdrew because of AE.

The TEAE that precipitated withdrawal among the study drug group were moderate in severity. These events include urticaria and rash (one subject each), vomiting and upper abdominal pain (one subject each). The remaining TEAE were local and include edema of the mouth or pharynx (three subjects), dry mouth, and throat irritation.

#### **6.6.13 Protocol VO61.08USA Reviewer's conclusions:**

Protocol VO61.08 met its primary efficacy endpoint, which was the daily CS during the pollen period while on treatment with the primary analysis done for the FAS. There was a decrease in CS of 28.2% in the study drug compared to the placebo group, with a lower 95% CI of 12.9%.

The incidence of AE in Protocol VO61.08USA was consistent with previous studies of this product. Most of these TEAE are mild or moderate in severity, and for some subjects, the moderate TEAE precipitated withdrawal from the study. There were no SAE that were related to the study drug, and there were no deaths in the study.

## **7. INTEGRATED OVERVIEW OF EFFICACY**

### **7.1 Indication #1**

ORALAIR® (5-grass pollen extract) sublingual tablet is indicated for the treatment of grass pollen-induced allergic rhinitis or conjunctivitis in adults, adolescents, and children (5 years of age and older) with a clinical history confirmed by positive skin test or in vitro testing for grass pollen-specific IgE antibodies.

#### **7.1.1 Methods of Integration**

In all natural field studies except for VO53.06, efficacy of the ORALAIR was evaluated over one grass pollen season. Therefore, the review across studies will discuss only efficacy for one year. Because the Phase 2 and 3 clinical trial efficacy data were not consistent, the overview of efficacy considers the totality of data across the clinical studies. Pooled efficacy data will not be reviewed.

As discussed in Section 6, the CS is the endpoint accepted by CBER for proof of efficacy. As noted in the synopses of each study and the table below, only the US study, VO61.08, used the CS as the primary endpoint. Therefore, integration depended upon post-hoc analyses of individual studies.

**Table 43. Summary of Protocols considered for the Integrated Study of Efficacy**

From original BLA application, Integrated Summary of Efficacy, Page 55

<b>Endpoint</b>	<b>VO34.04</b>	<b>VO61.08USA</b>	<b>VO52.06</b>	<b>VO53.06*</b>
Daily CS	<i>Post hoc analysis</i>	<b>Primary</b>	<i>Post hoc analysis</i>	<i>Post hoc analysis</i>
Daily RTSS	<i>Post hoc analysis</i>	Secondary	<i>Post hoc analysis</i>	<i>Post hoc analysis</i>
Daily RMS	<i>Post hoc analysis</i>	Secondary	<i>Post hoc analysis</i>	<i>Post hoc analysis</i>
Daily ASS	-	Secondary	-	-
ACS	<i>Post hoc analysis</i>	Secondary	Secondary	Secondary
ARTSS	<b>Primary</b>	Secondary	<b>Primary</b>	Secondary
ARMS	<i>Post hoc analysis</i>	Secondary	Secondary	Secondary
AASS	<i>Post hoc analysis</i>	Secondary	<i>Post hoc analysis</i>	<b>Primary</b>
RQLQ	Secondary	Secondary	-	Secondary
Global evaluation of treatment efficacy by patient	Secondary	Secondary	Secondary	Secondary

Review of each clinical trial of the study drug at a dose of 300 IR below shows that in each trial, the study drug group had a lower point estimate CS than placebo.

#### 7.1.2 Overview of Demographics and Baseline Characteristics |

Across studies, no notable differences in demographic characteristics were observed between the active and placebo treatment groups. Of note, the inclusion criterion of age differed among the non-pediatric studies: VO34.04, 18 to 45 years; VO61.08USA, 18 to 65 years; VO53.06, 18 to 50 years.

#### 7.1.3 Overview of Subject Disposition |

The subject disposition of each study is covered in Section 6. The percentages of subjects who failed screening, or who were lost to follow-up did not exceed the reviewer's expectations, and was consistent among studies. In essence, there are no signals from the review of subject disposition that impact negatively on the assessment of efficacy of the product.

#### 7.1.4 Overview of Analysis of Primary Endpoint(s) |

A comprehensive discussion of endpoints of AIT studies is presented at the beginning of Section 6. The CS for each clinical study, including Treatment Years 1-3 of Study VO53.06 are shown in Table 52.

**Table 44. CS in each efficacy trial of ORALAIR**

From original BLA application, Integrated Summary of Efficacy, Page 62

	Treatment	n	LS Mean	Percent change LS Mean relative to placebo Point estimate	Percent change LS Mean relative to placebo 95% CI
<b>Integrated analysis of all studies</b>	300 IR (4M)	663	0.41	-28.1%	-34.5%, -21.0%
<b>Integrated analysis of all studies</b>	Placebo	716	0.56		
<b>Integrated analysis of adult studies</b>	300IR (4M)	532	0.41	-26.1%	-33.8%, -18.8%
<b>Integrated analysis of adult studies</b>	Placebo	581	0.56		

The integrated analyses of these studies are shown below either as a comprehensive data set that includes children and adults (top), or only the adults. In both instances, the point estimate of the difference between study drug group and the placebo group is between -25% and -30%, a range that is considered clinically meaningful. Furthermore, pooling the data yielded a lower limit confidence intervals of ~20%, well beyond the 10% threshold defined by CBER.

**Table 45. Integrated analysis of efficacy of ORALAIR**

From original BLA application, ISE, Page 86

	Treatment	n	LS Mean	Percent change LS Mean relative to placebo Point estimate	Percent change LS Mean relative to placebo 95% CI
<b>Integrated analysis of all studies</b>	300 IR (4M)	663	0.41	-28.1%	-34.5%, -21.0%
<b>Integrated analysis of all studies</b>	Placebo	716	0.56		
<b>Integrated analysis of adult studies</b>	300IR (4M)	532	0.41	-26.1%	-33.8%, -18.8%
<b>Integrated analysis of adult studies</b>	Placebo	581	0.56		

#### 7.1.5 Overview of Secondary Endpoints

The secondary endpoints of most interest are the two parameters that contribute to the CS: the RTSS and the RMS. A clinically meaningful difference in the CS may result from heavily weighted differences in the RTSS with no differences in the RMS or vice-versa.

Tables 54 and 55 demonstrate that in the adult studies, that ORALAIR, 300 IR per day improved the point estimate change in RTSS less than the RMS. By contrast; for the pediatric study VO52.06, the RTSS was disproportionately improved. These weighted



differences may speak towards the preference of adults with ARC to use medication rather than withstand symptoms of the disease, particularly since the second generation antihistamines and topical products are easily tolerated with few side effects. Parents, by contrast, may be hesitant to treat children with medications. An additional possibility is that subjects with ARC who invest in the demands of a clinical study are those who are inherently more likely to use medication than the general population of affected individuals. In any event, the purpose of the CS is to take into account these behavioral variations among study subjects, and individual analyses of RTSS and RMS support the conclusion that ORALAIR is effective for the treatment of ARC.

**Table 46. RTSS in each efficacy study of ORALAIR**

From original BLA application, Integrated Summary of Efficacy p65

	Treatment	n	LS Mean	Percent change LS Mean relative to placebo Point estimate	Percent change LS Mean relative to placebo 95% CI
Study VO61.08USA <sup>b</sup>	300 IR (4M)	208	3.21	-22.9%	-38.2%, -7.5%
Study VO61.08USA <sup>b</sup>	Placebo	228	4.16		
Study VO34.04 <sup>b,d</sup>	300 IR (4M)	136	3.48	-29.2%	-43.4%, -15.1%
Study VO34.04 <sup>b,d</sup>	Placebo	148	4.91		
Study VO52.06 <sup>d</sup>	300 IR (4M)	131	2.52	-30.6%	-47.0%, -14.1%
Study VO52.06 <sup>d</sup>	Placebo	135	3.63		
Study VO53.06 Year 1 Treatment <sup>c,d</sup>	300 IR (4M)	188	0.56	-11.0%	-23.9%, 1.8%
Study VO53.06 Year 1 Treatment <sup>c,d</sup>	Placebo	205	0.67		

**Table 47. RMS in each efficacy study of ORALAIR**

From original BLA application, Integrated Summary of Efficacy, p68

	Treatment	n	LS Mean	Percent change LS Mean relative to placebo Point estimate	Percent change LS Mean relative to placebo 95% CI
Study VO61.08USA <sup>b</sup>	300 IR (4M)	208	0.11	-46.5%	-73.9%, -19.2%
Study VO61.08USA <sup>b</sup>	Placebo	228	0.20		
Study VO34.04 <sup>b,d</sup>	300 IR (4M)	136	0.41	-30.1%	-49.5%, -10.6%
Study VO34.04 <sup>b,d</sup>	Placebo	148	0.59		
Study VO52.06 <sup>d</sup>	300 IR (4M)	131	0.46	-29.5%	-50.9%, -8.0%
Study VO52.06 <sup>d</sup>	Placebo	135	0.65		
Study VO53.06 Year 1 Treatment <sup>c,d</sup>	300 IR (4M)	188	0.49	-22.5%	-38.0%, -7.0%
Study VO53.06 Year 1 Treatment <sup>c,d</sup>	Placebo	205	0.63		

7.1.6 Overview of other Endpoints |

Exploratory and additional endpoints have little impact on the evaluation of the product and will not be addressed in the Integrated Analysis of Efficacy.

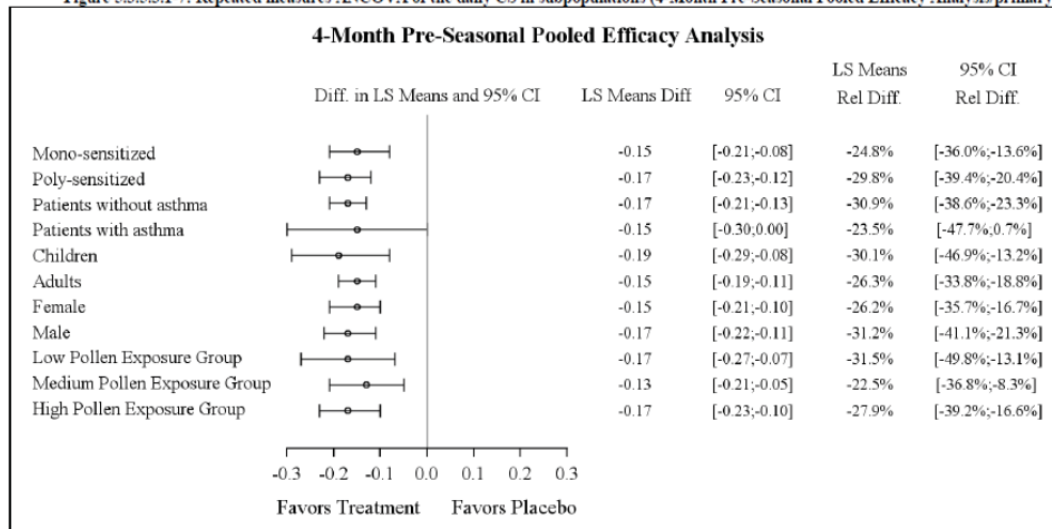
7.1.7 Overview of subpopulations |

In the clinical studies, there were no significant differences in efficacy among children and adults; males and females; and among subjects who lived in areas with low, medium, or high pollen levels. There were also no differences 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 to cat or dog allergens). Importantly, subjects who were allergic to seasonal or perennial allergens to which exposure may overlap with grass pollen were excluded from these studies. Subjects who were sensitive to tree or weed pollens, or to house dust mites were excluded, as were subjects who were pet allergic and have pets in the home. Therefore, the term “poly-sensitized” is much more restricted in the context of these studies than usual. Similarly, while there were no significant differences in efficacy between: subjects with and without asthma; only subjects with mild asthma that requires intermittent rescue medication were included in the study. (Table 43)

**Figure 20. Efficacy in subpopulations**

From original BLA application, Integrated Summary of Efficacy p102

Figure 5.3.5.3.1-7: Repeated measures ANCOVA of the daily CS in subpopulations (4-Month Pre-Seasonal Pooled Efficacy Analysis/primary analysis set)



Source: [Table 5.3.5.3.1-50](#), [Table 5.3.5.3.1-51](#), [Table 5.3.5.3.1-52](#), [Table 5.3.5.3.1-53](#) and [Table 5.3.5.3.1-54](#)

7.1.8 Overview of Persistence of Efficacy |

Persistence of efficacy was measured only in one trial, VO53.06, in which subjects were treated for three years and observed for two additional years. As discussed in Section 6.3, post-hoc analysis of the CS showed a difference between the study drug groups and the placebo group in Year 4, the first observational year after treatment Years 1-3. These differences met CBER’s criteria of an upper bound 95% CI < -10% for the study drug

group that was treated for 2 months prior to GPS, but not for the study group that was treated 4 months prior to GPS. These differences were not sustained in Year 5, the second observational year.

#### 7.1.9 Product-Product Interactions |

|There are no product-product interactions to consider.

#### 7.1.10 Additional Efficacy Issues/Analyses |

|There are no additional efficacy issues or analyses.

#### 7.1.11 Efficacy Conclusions |

|The primary endpoints of each study considered in this review consist either of symptom scores or combined medication and symptom scores. The relevant secondary endpoints discussed in this review are those that contribute to the combined scores, the RTSS and the RMS. As discussed in Section 6, CBER asserts that CS is the best available endpoint to assess allergen immunotherapy for ARC. Overall, the reviewer agrees with the sponsor's assertion that ORALAIR is effective for immunotherapy of ARC due to grass allergy.

Efficacy was tested in subjects allergic to pollens from grasses that are not cross-reactive with components of the 5-grass mixture, or to pollens that present in the environment during grass pollen season. Each of these studies excluded subjects who are allergic to the most common tree and weed pollen allergens (such as oak and ragweed, respectively), or who are allergic to Johnson, Bahia, or Bermuda grass pollen. Since these grasses pollinate during the same time period as those included in the 5-grass mixture, subjects who are allergic to these grass pollens, as well as those who are allergic other pollens that may overlap with grass may not experience reduction of grass allergy symptoms to the same degree as those in the study populations.

## | **8. INTEGRATED OVERVIEW OF SAFETY** |

### | **8.1 Safety Assessment Methods** |

|As indicated in each of the study synopses, safety was assessed through the use of daily diary cards and monitoring during study visits.

### **8.2 Safety Database**

Across clinical trials 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  $\geq 18$  years of age at entry who received ORALAIR at a daily dose of 300 IR or placebo (includes adults enrolled in seven studies)
- 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.

#### 8.2.1 Studies/Clinical Trials Used to Evaluate Safety |

The pool of studies that comprise the Full Safety Set (FSS) is shown in Table 4, Section 5.3.

#### 8.2.2 Overall Exposure, Demographics of Pooled Safety Populations |

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.

#### 8.2.3 Categorization of Adverse Events |

AE for any drug or biologic may be categorized by criteria such as severity (mild, moderate or severe) on the basis of quality of life. Serious AE are appropriately defined. In addition, AE associated with allergen immunotherapy are categorized as local or systemic.

AE are divided by organ class according to the MedDRA classification, which is of limited use because subjects who experience local application reactions generally experience events assigned to the GI system (oral pruritus) and respiratory system (throat irritation). Furthermore, certain events assigned to each system may indicate one and the same event-- palatal edema (GI system) and pharyngeal edema (respiratory system), for example.

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

There are no caveats introduced by pooling safety data across studies or clinical trials.

## 8.4 Safety Results

### 8.4.1 Deaths

There were no deaths in any of the studies.

### 8.4.2 Nonfatal Serious Adverse Events

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

There were no episodes of anaphylaxis or anaphylactic shock in the clinical safety database. However, severe laryngopharyngeal disorders are a risk of sublingual immunotherapy. There were a total of three TEAE of concern that were laryngopharyngeal disorders, of which two were categorized as SAE; all three of these events led to premature study withdrawal.

- 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. This event was considered an SAE.
- 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. This event was considered an SAE.
- A severe pharyngolaryngeal edema was reported in Subject 001/031 who received 500 IR of ORALAIR in Study VO33.04 DK five minutes after the first intake of immunotherapy. The symptoms (i.e., throat irritation, oropharyngeal swelling and ear pruritus) occurred intermittently over approximately 24 hours. The following day, the subject reported swollen tongue and tongue blistering five minutes after receiving the second 500 IR dose. The symptoms occurred intermittently and lasted over approximately 13 hours and 25 minutes, respectively. This event resolved on this day after treatment with prednisolone 50 mg and fexofenadine hydrochloride 180 mg.

In addition, an additional SAE 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.

All other SAE in the clinical studies, including the single SAE reported in the pediatric study, were considered “unlikely” or “not related” to the study drug.

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

The first study was conducted in 2008 and included a total of 808 adults and 91 children and adolescents who were treated with ORALAIR. The 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 summary submitted to the BLA, SAE were reported in six 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

The second study was conducted in 2009, and included a total of 829 patients (457 children between 5 and 11 years old and 372 adolescents between 12 and 17 years old) who were treated with ORALAIR. The 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, SAE were reported in six 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

With the exception of the episode of Samter's triad, all of these serious adverse events were considered related to ORALAIR administration.

#### 8.4.3 Study Dropouts/Discontinuations |

|In the adult pooled analysis, 4.7% (49/1038) of adult 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 30<sup>th</sup> 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.

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.

#### 8.4.4 Common Adverse Events

Overall, 76.9% of subjects in the study drug groups and 69.8% of subjects in the placebo group experienced AE. The high baseline incidence of upper respiratory infections and allergic symptoms accounts for the similarity between the study drug and placebo group.

In the adult studies, 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). Other TEAEs reported in >2.5% of ORALAIR recipients and at a higher frequency than placebo recipients included mouth, lip, tongue, or pharyngeal edema, tongue, ear or eye pruritus, oral paresthesia, dyspepsia, sneezing, cough, rhinorrhea, nasal discomfort, oropharyngeal pain, allergic rhinitis, rhinitis, eye pruritus, increased lacrimation, or conjunctivitis.

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 those listed in the above study, as well as asthma, abdominal pain, vomiting, tonsillitis, bronchitis, upper respiratory tract infection, atopic dermatitis, and pyrexia. 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).

#### 8.4.5 Clinical Test Results

In a subset of subjects, peripheral blood eosinophil counts and serum allergen (grass) specific IgE transiently rise and then fall towards baseline. These events are known responses to immunotherapy. Often allergen-specific serum IgG<sub>4</sub> will rise as IgE is falling. While the rise in IgG<sub>4</sub> is known to accompany successful immunotherapy, it is not a biomarker for efficacy.

#### 8.4.6 Systemic Adverse Events

Urticaria or a systemic rash may occur with SLIT. The incidence of each of these was no different in the study group and placebo arms of all study subjects. There were no episodes of anaphylaxis or anaphylactic shock.

From a broad standardized MedDRA query search for anaphylactic reaction after licensure in the European Union, 24 serious reports were retrieved. Upon review, four 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.

#### 8.4.7 Local Reactions

Local reactions observed during the clinical studies are discussed extensively above. From a standardized MedDRA query search after licensure in the European Union, a broad list of preferred terms suggestive of severe laryngopharyngeal reactions retrieved 46 cases. 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 they either did not correspond to a severe laryngopharyngeal disorder or were not considered related to ORALAIR by both the reporter and the applicant. The remaining 11 cases (8 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.

#### 8.4.8 Adverse Events of Special Interest

AESI are anaphylaxis and local effects to the oropharynx that obstruct the airway. These are discussed above.

### 8.5 Additional Safety Evaluations

None

#### 8.5.1 Dose Dependency for Adverse Events

Allergen exposure in allergic individuals causes allergic responses. It is therefore inherent that allergen immunotherapy with unmodified allergens is limited by dose. The sponsors demonstrated that the 100 IR dose elicits fewer side effects, but is ineffective, the 500 IR dose is poorly tolerated, and the 300 IR dose is better tolerated, but associated with more AE than the 100 IR dose. Except for the ramp-up period, 300 IR is the only dose that is under consideration for approval.

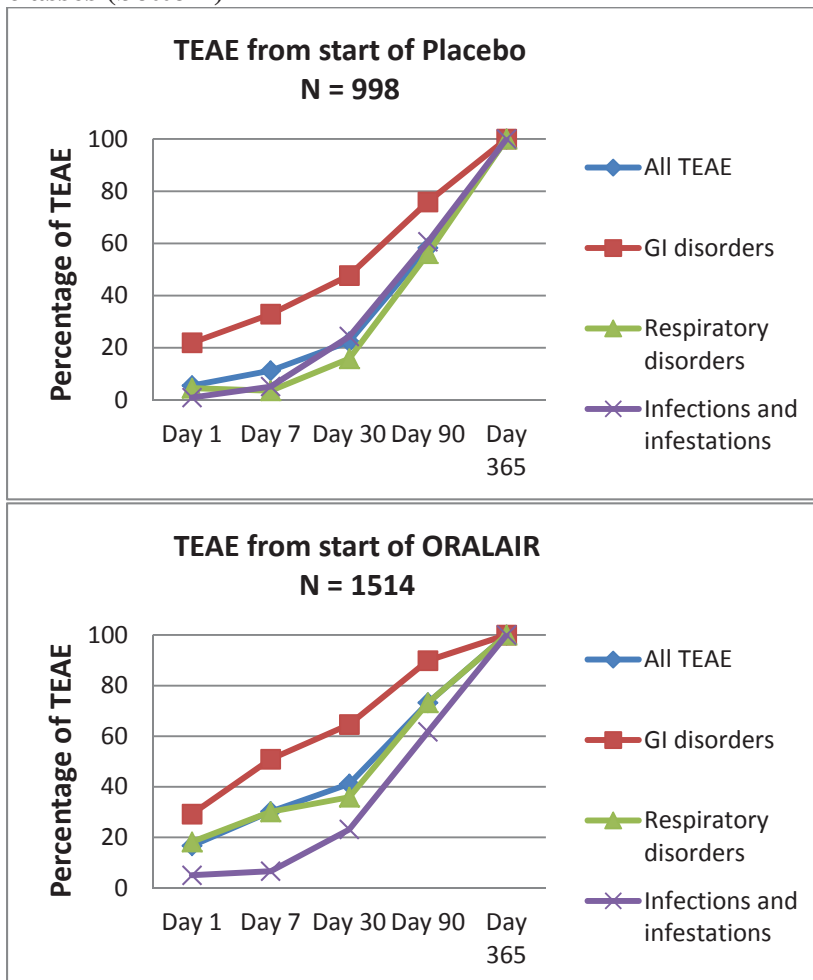


### 8.5.2 Time Dependency for Adverse Events

The TEAE are allergic responses, which may be divided into early (within minutes) and late (within hours) phase, relative to the time of allergen exposure (treatment). The local and systemic TEAE that are associated with this product are early phase events and occur within minutes of exposure.

With regard to time from initiation of therapy, Figure 20 shows that 20-25% of respiratory and GI events (local application reactions are included in both MedDRA classes) occur on Day 1 of therapy, and 70-90% of TEAE occur by Day 90. Data from the multiyear Study VO53.06 indicate a much lower incidence of local application site reactions, and no systemic reactions in the second and third years of therapy.

**Figure 21. Cumulative frequency of all TEAE (top), and for specific MedDRA organ classes (bottom)**



Adapted from original BLA 125471, Summary of Clinical Safety

### 8.5.3 Product-Demographic Interactions

None

#### 8.5.4 Product-Disease Interactions

None

#### 8.5.5 Product-Product Interactions

None

Insert text here

#### 8.5.6 Human Carcinogenicity

There is no evidence in animal toxicity studies or in human studies that allergen immunotherapy, whatever the route, is carcinogenic.

#### 8.5.7 Overdose, Drug Abuse Potential, Withdrawal, and Rebound |

[There is limited potential for an allergic subject to harm him/herself by taking multiple tablets. This would require opening multiple blister packs and simultaneous sublingual administration of multiple tablets. There is no potential for abuse or withdrawal effects.

#### 8.5.8 Immunogenicity (Safety) |

[There is no evidence that there is adverse immunogenicity of this product or associated with immunotherapy in general. Insert text here

#### 8.5.9 Person-to-Person Transmission, Shedding

Not applicable.

### **8.6 Safety Conclusions.**

For the majority of subjects who participated in the clinical trials and the post-marketing studies, ORALAIR was well tolerated and safe. There were no episodes of anaphylaxis in the clinical studies, and there were no treatment-associated deaths in the clinical or post-marketing studies.

ORALAIR causes local application reactions that may be severe or serious; most but not all of these occurred on Day 1 of treatment, which takes place in the health care setting. Postmarketing data suggest that life-threatening local and allergic reactions may occur beyond Day 1, particularly in subjects who will be part of the patient population, but were excluded from the clinical studies. These subjects include those with moderate or severe asthma who are on daily inhaled corticosteroids, and subjects with underlying cardiac or other pulmonary disease.

Therefore, the clinical reviewer recommends that ORALAIR should be co-prescribed with auto-injectable epinephrine. The potential for severe or serious local reactions and anaphylaxis should be stated in the package insert as a boxed warning. In addition, a Medication Guide should be distributed with the prescription to insure that patients are aware of the risk of these reactions at home, and are educated towards the self-administration of epinephrine with an auto-injectable device.

## 9. ADDITIONAL CLINICAL ISSUES

### 9.1 Special Populations |

#### 9.1.1 Human Reproduction and Pregnancy Data |

There are no data regarding human reproduction or pregnancy. Based on animal toxicity data, the product will be placed in Pregnancy Category B.

ORALAIR likely safe for women who become pregnant while undergoing SLIT. Despite inclusion criteria that required adequate methods of birth control, there were pregnancies in the clinical studies of this protocol. There was no evidence that the product harmed the fetus. Whether initiating SLIT in pregnant subjects affects the risk profile of the product has not been studied.

#### 9.1.2 Use During Lactation

Nursing mothers were excluded from the study, and the product was discontinued if a female who became pregnant chose to carry the fetus to term. Therefore, the effect of the product during lactation is unknown.

#### 9.1.3 Pediatric Use and PREA Considerations |

A small cohort of children 5-17 years of age was studied in Protocol VO52.06. Efficacy data from this study were similar to the efficacy data acquired in adult subjects. A small set of children 12-17 years of age were also included in Protocol VO60.08, and safety data from these two studies reflected safety data acquired from adult subjects.

The product was presented to PeRC on March 19, 2014.

- PeRC waived PREA requirements for children below five years of age, as seasonal environmental allergies are unusual in this age group.
- PeRC agreed with the plan of a safety study of children 5-9 years of age.

#### 9.1.4 Immunocompromised Subjects

Efficacy of the product requires a competent immune system. Immunocompromised subjects were excluded from the studies. The product is not expected to be used in immunocompromised subjects, and should be contraindicated in the absence of a competent immune system.

#### 9.1.5 Geriatric Use

The product has not been studied in subjects greater than 65 years of age. Consequently the indications for adults must be limited to those who are 18-65 years of age.

### 9.2 Aspect(s) of the Clinical Evaluation Not Previously Covered |

None

## 10. CONCLUSIONS

ORALAIR, 300 IR per dose, is safe and effective for immunotherapy of allergic rhinoconjunctivitis due to sensitivity to any combination of the five grass pollens included in the product for patients 10-65 years of age. Subjects who are allergic to grass pollens that do not cross-react with those in ORALAIR, or subjects who are allergic to other pollens in the environment during grass pollen season may not experience the level of treatment effect experienced by the study subjects.

The first tablet must be taken in the office of a health care provider who is experienced in the treatment of life threatening allergic reactions, including those that may occlude the upper airway and systemic anaphylaxis.

The dosage for children is 100 IR the first day, 200 IR the second day, and 300 IR the third day and thereafter. The dosage for adults is 300 IR per day. Patients should be educated as to the potential risk of life-threatening laryngopharyngeal application site reactions, and be educated in the use of an epinephrine administration device. The risk of SAE and severe AE may decrease with longer treatment times (such as > 6-12 months), but this must be confirmed with a safety data base much larger than currently available.

## 11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

### 11.1 Risk-Benefit Considerations

#### Table 48. Risk-Benefit Table

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
<p><b>Analysis of Condition</b></p>	<ul style="list-style-type: none"> <li>The symptoms of ARC are runny or stuffy nose, excessive tearing, itchy or scratchy throat</li> <li>Seasonal ARC is caused by allergic sensitivity to seasonal environmental allergens, such as grass pollens</li> <li>ARC is common in US pediatric and adult populations</li> <li>ARC impacts on quality of life including lost work and school days</li> <li>ARC in children may resolve, or it may progress to include allergic asthma</li> <li>ARC may be treated with pharmacologic therapy, such as nasal steroids, or topical or systemic antihistamines</li> <li>Pharmacologic therapy is sufficient for a subset of mildly affected ARC patients</li> <li>When pharmacologic therapy is insufficient, immunotherapy may improve quality of life</li> <li>Subcutaneous immunotherapy (SCIT) is the current mode of administration of Immunotherapy in the US. SCIT must be administered in a health care setting, and requires frequent visits (every 2-4 months); many patients who may benefit from immunotherapy opt out of SCIT</li> <li>For a substantial majority of patients, SLIT may be safely self-administered at home</li> </ul>	<ul style="list-style-type: none"> <li>ARC is highly prevalent in US populations</li> <li>ARC impacts on quality of life</li> <li>In a subset of patients, ARC precedes and contributes to allergic asthma</li> </ul>
<p><b>Unmet Medical Need</b></p>	<ul style="list-style-type: none"> <li>The totality of data suggests that ORALAIR improves grass-pollen induced ARC symptoms and medication use by about 25%, which is above the threshold that impacts upon quality of life</li> <li>While the totality of data supports the conclusion of efficacy of ORALAIR, at least one individual study failed to demonstrate improvement.</li> <li>It is uncertain whether the treatment effect of ORALAIR is maintained beyond after one or multiple courses of treatment. The single long-term study performed in the EU suggested that benefit of ORALAIR may be maintained for a fourth year beyond three years of therapy, but not for a fifth year.</li> </ul>	<ul style="list-style-type: none"> <li>Because of the convenience of SLIT administration, its availability is expected to increase the use of immunotherapy to treat ARC</li> <li>ORALAIR may increase the use of immunotherapy in grass pollen allergic US patients, and significantly impact on overall quality of life in this population</li> </ul>
<p><b>Clinical Benefit</b></p>	<ul style="list-style-type: none"> <li>The totality of data suggests that ORALAIR improves grass-pollen induced ARC symptoms and medication use by about 25%, which is above the threshold that impacts upon quality of life</li> <li>While the totality of data supports the conclusion of efficacy of ORALAIR, at least one individual study failed to demonstrate improvement.</li> <li>It is uncertain whether the treatment effect of ORALAIR is maintained beyond after one or multiple courses of treatment. The single long-term study performed in the EU suggested that benefit of ORALAIR may be maintained for a fourth year beyond three years of therapy, but not for a fifth year.</li> </ul>	<ul style="list-style-type: none"> <li>The totality evidence for clinical benefit of ORALAIR suggests 20-25% improvement in symptoms, medication use, or both.</li> <li>Treatment effects of ORALAIR taken for three consecutive years (with breaks in therapy of about 3-4 months after the end of grass pollen season) may be sustained for one additional year.</li> </ul>
<p><b>Risk</b></p>	<ul style="list-style-type: none"> <li>The most substantial risks of ORALAIR are life threatening local or systemic allergic reactions. These are most common, but may not be restricted to the first day of treatment, which should be administered in a health care setting.</li> <li>Risk of severe and serious adverse events may decrease in the second and subsequent treatment years.</li> <li>The most common risks are mild to moderate application site reactions, including itching or swelling to the back of the throat, tongue, or mouth</li> <li>There is a theoretical risk of eosinophilic esophagitis in those who do not allow the tablet to dissolve beneath the tongue and swallow the tablet instead.</li> <li>The clinical study population had substantially less morbidity than patients who will be prescribed ORALAIR. In particular, this includes patients with moderate to severe asthma, and those with underlying cardiac and non-asthmatic pulmonary disease.</li> <li>ORALAIR has not been studied in adults &gt; 65 years of age</li> </ul>	<ul style="list-style-type: none"> <li>Overall, the benefit of ORALAIR outweigh the risks</li> <li>The first tablet must be taken in the office of a health care provider who is experienced in the treatment of life threatening allergic reactions, including those that may occlude the upper airway and systemic anaphylaxis.</li> <li>Patients should be educated as to the potential risk of life-threatening laryngopharyngeal application site reactions, and be educated in the technique of epinephrine self-administration; the device should be co-prescribed with ORALAIR.</li> <li>If ORALAIR is approved, it will be indicated for patients 5-65 years of age.</li> </ul>
<p><b>Risk Management</b></p>	<ul style="list-style-type: none"> <li>ORALAIR may result in severe or serious laryngopharyngeal reactions or systemic allergic reactions. Most often, these will occur on Day 1 of therapy.</li> </ul>	<ul style="list-style-type: none"> <li>If ORALAIR is approved for patients 10-65 years of age, the package insert should include a boxed warning of the potential of serious local or systemic reactions, and a medicine guide would have to be distributed to all patients.</li> <li>The first dose is taken in the office of a health care provider who is experienced in the treatment of allergic reactions. The first dose of ORALAIR for adults should be 300 IR, so that patients who are likely to experience life threatening reactions do so in the health care setting rather than at home after ramp-up.</li> </ul>

### **11.2 Risk-Benefit Summary and Assessment**

Data submitted to the BLA establish that treatment of patients 10-65 years of age with ORALAIR may decrease the symptoms of ARC and significantly improve quality of life in patients with ARC.

Clinical data indicate that the overwhelming majority of patients will tolerate ORALAIR with mild or moderate AE due to local application reactions. A subset of patients who experience mild to moderate local application reactions will discontinue treatment because of discomfort rather than risk. Based on clinical studies and post-marketing analysis, the data indicate that 0.1-0.5% of subjects will experience severe or serious laryngopharyngeal or systemic reactions. Most, but not all of these will be associated with the first treatment exposure to ORALAIR.

### **11.3 Discussion of Regulatory Options**

The clinical reviewer recommends that the ORALAIR 300 IR be approved for the treatment of ARC with or without mild asthma. Children and adolescents are to take 100 IR the first day, 200 IR the second day, and 300 IR the third day and thereafter as this was the dosage regimen in the pediatric studies.

The regimen studied in the adult studies was 300 IR on the first day and thereafter with no “ramp-up.” The sponsor proposed to amend the dosage regimen to include the ramp-up for adults but the clinical reviewer recommends reject the proposed amendment because the ramp-up may have the unintended consequence of a patient experiencing a life-threatening reaction to ORALAIR upon reaching the full dose at home, rather than taking the full dose on Day 1 in the health care setting.

### **11.4 Recommendations on Regulatory Actions**

1. I recommend approval of ORALAIR for children and adults 10-65 years of age for treatment of ARC with or without mild asthma.
2. The dosage for children should be 100 IR on the first day, 200 IR the second day, and 300 IR thereafter. The dosage for adults should be 300 IR each day without a ramp-up.
3. The first dose of ORALAIR should be taken in the health care setting.
4. The package insert should include a boxed warning of the potential of serious local or systemic reactions, and a medicine guide would have to be distributed to all patients.

### **11.5 Labeling Review and Recommendations**

1. The trade name is ORALAIR®. The Product Proper Name is Sweet Vernal, Orchard, Perennial Rye, Timothy, and Kentucky Blue Grass Mixed Pollens Allergen Extract Tablet for Sublingual Use.
2. 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 10 to 65 years of age.

3. The dose of the sublingual tablets is 300 IR each day. Children will take 100 IR the first day, 200 IR the second day, and 300 IR thereafter.
4. The Package Insert should include a boxed warning of the potential of serious local or systemic reactions, and a medicine guide to be distributed to all patients.

### **11.6 Recommendations on Postmarketing Actions**

The sponsor proposes to continue routine Pharmacovigilance in accordance with ICH Guidance E2E. Expedited AE and periodic safety reports will be submitted to FDA in compliance with US 21 CFR 600.80 and any other applicable US requirements. These events are subject to enhanced surveillance reports.

In addition, the following post-marketing studies will be performed (approved by review team):

- An open label study in ~300 children 5 - 9 years of age who are allergic to grass pollens contained in ORALAIR. Subjects will receive ORALAIR for 30 days and will be followed for the occurrence of local and systemic adverse events (AEs) that result in medical attention (e.g., epinephrine use, hospitalization, and/or an ER visit). In addition, potential risk factors for any AEs that occur should be assessed as secondary objectives based on information obtained in evaluation of events. Such risk factors would include, but not be limited to month of year when event occurs, age, antecedent interruption of therapy, and use of any concomitant medication including allergen immunotherapy. AEs will be monitored by a diary card that will survey for specific events.
- A Phase 4 safety study of 6,000 patients 10-65 for 30 days to survey for AE. The study population will be patients who are prescribed ORALAIR in the European Union and the US. Patients will be followed for the occurrence of local and systemic adverse events (AEs) that result in medical attention (e.g., epinephrine use, hospitalization, and/or an ER visit). In addition, potential risk factors for any AEs that occur should be assessed as secondary objectives based on information obtained in evaluation of events. Such risk factors would include, but not be limited to month of year when event occurs, age, antecedent interruption of therapy, and use of any concomitant medication including allergen immunotherapy. AEs will be monitored by a diary card that will survey for specific events.

#### Allergic Reactions (including severe laryngopharyngeal disorders)

Clinical data and four years of Postmarketing experience have shown the majority of reported adverse events to be related to allergic reactions. These allergic reactions include application site reactions linked to the route of administration (sublingual) and are of mild to moderate severity. More severe allergic reactions, such as severe laryngopharyngeal disorders or anaphylactic shock, considered as class-effects, have been identified as risks requiring further evaluation. To date, no case of anaphylactic shock has been reported with ORALAIR.

The sponsor uses enhanced reporting via a specialized reporting form and a focused list of MedDRA PTs to periodically screen and analyze reports of severe laryngopharyngeal disorders. An “anaphylactic reaction” standardized MedDRA Query (SMQ) is run periodically to identify and screen potential cases.

#### Autoimmune Disease

A theoretical class-wide (oral allergenics for sublingual immunotherapy) concern is that ORALAIR may induce or potentiate autoimmune disorders has also been identified, although current review of literature and post-marketing experience do not indicate an association between any autoimmune disorders and allergen immunotherapy.

Given the complexity of evaluating potential autoimmune diseases, developing a list of autoimmune-related PTs was not considered feasible, and instead, special focus will be given to any cases related to autoimmune diseases or potential signs of autoimmune disorder.

#### Risk Management / Risk Evaluation and Mitigation Strategy (REMS)

No REMS or similar non-US action has been undertaken for this product; none is contemplated following US licensure.

CBER agrees with the proposed plan. |