Application Type	Original BLA
STN	125471
CBER Received Date	December 18, 2012
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Division / Office	CBER/OBE/DB/VEB
Priority Review	n/a
Reviewer Name(s)	Tammy J. Massie, PhD
Review Completion Date / Stamped Date	Feb. 12, 2014
Supervisory Concurrence	A. Dale Horne, DrPH, Branch Chief VEB Lihan Yan, PhD, Team Leader BAT
Applicant	Stallergenes, Inc.
Established Name	Sweet Vernal, Orchard, Perennial Rye, Timothy, and Kentucky Blue Grass Mixed Pollens Allergen Extract
(Proposed) Trade Name	Oralair®
Pharmacologic Class	Allergenic Extract (Grass)
Formulation(s), including Adjuvants, etc	Tablet
Dosage Form and Route of Administration	Sublingual (placed under tongue until dissolved)
Dosing Regimen	300 IR (index of reactivity) per tablet, once per day with 100 IR, 200 IR and 300 IR the first three days of administration, respectively.
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. Oralair® is approved for use in persons 10 to 65 years of age.

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GLOSSARY

2M	Patients received active treatment starting 2 months prior to the pollen season
4M	Patients received active treatment starting 4 months prior to the pollen season
AASS	Average Adjusted Symptom Score
ASS	Adjusted Symptom Score
ACS	Average Combined Score
ANCOVA	Analysis of Covariance
ARIA GA2LEN	Allergic Rhinitis and its Impact on Asthma Global Allergy and Asthma European Network
ARMS	Average Rescue Medication Score
ARTSS	Average Rhinoconjunctivitis Total Symptom Score
AUC	Area Under the Curve
BMI	Body Mass Index
CA	Complementary Analysis
CI (or % CI)	Confidence Interval (or % Confidence Interval)
CID	Clinically Important Difference
CMH	Cochran-Mantel-Haenszel
CS	Combined Score
CSR	Clinical Study Report
DRM	Data Review Meeting
DSMB	Data and Safety Monitoring Board
EMA	European Medicines Agency
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
GES	Global Evaluation Score
GLM	Generalized Linear Model
ICH	International Conference on Harmonisation
Ig	Immunoglobulin
IR	Index of Reactivity
ITT	Intention-To-Treat
LS	Least Squares
LOCF	Last Observation Carried Forward
MCID	Minimal Clinically Important Difference
MIVQUE0	Minimum Variance Quadratic Unbiased Estimation
ML	Maximum Likelihood
ND	Not Determined
NS	Not Significant
PP	Per Protocol
PPS	Per Protocol Set
PRO	Patient-Reported Outcome
RC	Rhinoconjunctivitis

REML	Restricted Maximum Likelihood
RMS	Rescue Medication Score
RQLQ	Rhinoconjunctivitis Quality of Life Questionnaire
RRTSS	Retrospective Rhinoconjunctivitis Total Symptom Score
RTSS	Rhinoconjunctivitis Total Symptom Score
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SD	Standard Deviation
SEM	Standard Error of the Mean
SLIT	Sublingual Immunotherapy
SIT	Specific Immunotherapy
TEAE	Treatment Emergent Adverse Event
VO	Voie Orale (i.e., oral route in French)
WAO	World Allergy Organization
[0-4] hours	From 0 to 4 hours with 0 excluded and 4 included

1. EXECUTIVE SUMMARY

Stallergenes conducted a multinational clinical development program for ORALAIR® (5-grass pollen extract) sublingual tablet for the treatment of allergic rhinoconjunctivitis in patients with clinical symptoms due to grass pollen allergy.

ORALAIR® contains allergen extracts of the following five grass pollens: Kentucky bluegrass (*Poa pratensis* L.), Orchard (*Dactylis glomerata* L.), Perennial rye (*Lolium perenne* L.), Sweet vernal (*Anthoxanthum odoratum* L.) and Timothy (*Phleum pratense* L.).

Overall, 2,512 patients participated in the clinical development program of Oralair®, which consisted of eight clinical trials. The effectiveness of Oralair® was evaluated in six randomized, double-blind, placebo-controlled clinical trials:

- VO34.04 (European study-in Adults),
- VO61.08US (US study-in Adults),
- VO56.07A (Allergen exposure chamber study-in Adults),
- VO52.06 (Pediatric study-in Adolescents and Children),
- VO53.06 (Long Term study-in Adults), and
- VO60.08 (Alternate regimen study-in Adults, Adolescents and Children)

Two additional studies in adults: VO33.04DK (N=30) and VO40.05, (an extension of study VO34.04), consisted of only safety and tolerability data.

A summary of the six efficacy studies is provided in Table 1 below:

Table 1: Summary of Studies that examined the Safety, Tolerability and Efficacy of Oralair®

Study #	Study title	Study objective	Duration of treatment preseasonal/coseasonal	Treatment arms	Number of exposed patients	Score	Primary Endpoint Point est/ Relative LS Mean Diff. *vs* Placebo	Statistical sign *vs* Placebo (p)
VO34.04	Randomized, double-blind, placebo-controlled, multinational, multi-centre, Phase IIb/III study of the efficacy and safety of three doses of sublingual immunotherapy (SLIT) administered as tablets once daily to patients suffering from grass pollen rhinoconjunctivitis	Efficacy, Safety in adults	Approximately 4 months pre-seasonally and ≥ 1 month co-seasonally[a]	500 IR (4M) 300 IR (4M) 100 IR (4M) Placebo	160 155 157 156	ARTSS	-1.22/ND -1.39/ND -0.26/ND	0.0006 0.0001 0.4606
VO61.08US	A randomized, double-blind, placebo-controlled, multi-centre, Phase III study of the efficacy and safety of 300 IR sublingual immunotherapy (SLIT) administered as allergen-based tablets once daily to adults patients suffering from grass pollen rhinoconjunctivitis	Efficacy, Safety in adults	Approximately 4 months pre-seasonally and ≥ 1 month co-seasonally[a]	300 IR (4M) Placebo	233 240	Daily CS	-0.13/-28.2%	0.0003
VO56.07A	A randomised, 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 300 IR allergen-based tablets once daily to adults suffering from grass pollen rhinoconjunctivitis	Efficacy, Safety in adults	Approximately 4 months (out of the pollen season)	300 IR Placebo	45 44	ARTSS	-1.97/ND	0.0003
VO52.06	A randomised, double-blind, placebo- controlled, multinational, multi-centre, Phase III paediatric study of the efficacy and safety of 300 IR sublingual immunotherapy (SLIT) administered as allergen-based tablets once daily to children suffering from grass pollen rhinoconjunctivitis	Efficacy Safety in patients under 18 y.o.	Approximately 4 months pre-seasonally and ≥ 1 month co-seasonally[a]	300 IR (4M) Placebo	139 139	ARTSS	-1.13/ND	0.0010
VO53.06	A randomised, double-blind, placebo-controlled, multinational, multi-centre, 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 patients suffering from grass pollen rhinoconjunctivitis	Sustained efficacy[b], Post-Rx efficacy, Safety in adults	Approximately 4 months pre-seasonally and ≥ 1 month co-seasonally for 3 consecutive grass pollen seasons	300 IR (4M) 300 IR (2M) Placebo	207 207 219	AASS (Year 3)	-1.82/-34.9% -1.96/-37.6%	<0.0001 <0.0001
VO60.08	A randomised, 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 patients suffering from grass pollen rhinoconjunctivitis (with or without asthma)	Efficacy, Safety in adults and adolescent	Approximately 2 months pre-seasonally and ≥ 1 month co-seasonally[a]	300 IR (2M) Placebo	188 193	AASS	-0.49/-8.1%	0.2344

AASS = Average Adjusted Symptom Score; ARTSS = Average Rhinoconjunctivitis Total Symptom Score; CS = Combined Score; LS = Least Squares; ND = Not Determined; SLIT = Sublingual Immunotherapy; 300 IR (4M) = patients received active treatment starting 4 months prior to the pollen season; 300 IR (2M) = patients received active treatment starting 2 months prior to the pollen season
Source: Adaptation of Clinical Study Report BLA 125471/0000 2.7.6.1 TABULAR LISTING OF CLINICAL STUDIES page 2

The studies provided in this submission appear to support the applicant's conjecture that the Oralair® 300 IR product is safe and effective in the treatment of allergic rhinoconjunctivitis, using the Agency's pre-specified criterion for efficacy based on the Combined Symptom score that incorporates both rescue medication and symptom scores. Furthermore, similar positive trends are observed for the individual endpoints of Daily Symptom Scores as well as the Daily Rescue Medication Scores.

Based on the data submitted and reviewed, Oralair®, 300 IR per dose, appears to be safe and effective for immunotherapy of allergic rhinoconjunctivitis due to sensitivity to any combination of the five grass pollens included in the product. The product appears to be safe and effective for adults 10-65 years of age, based on the statistical analyses examined and performed by the reviewing statistician.

2. CLINICAL AND REGULATORY 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 Unites States. Untreated or inadequately treated ARC can cause 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 when at work.

Currently treatments for ARC include allergen avoidance, pharmaceutical treatment options including pharmacologic therapy such as oral antihistamines and nasal corticosteroids (which provide temporary relief from allergy symptoms but are not effective in all patients, and are not disease-modifying), and administration is subcutaneous injection (SCIT) (which is a treatment that modifies the immune response and treats the cause rather than the symptoms).

An alternative to SCIT is sublingual immunotherapy (SLIT) in which treatment is administered orally rather than by injection. Two items to note with SLIT treatment presented in the literature include 1). the incidence of severe or serious AE associated with SLIT is significantly lower than with SCIT such that SLIT may be self-administered at home by the patient, and 2). safe use of SCIT requires administration in a clinic that is capable of responding to systemic allergic reactions.

Stallergenes SA (the applicant) is a French biopharmaceutical corporation that focuses on the treatment of allergic disease. In Europe, Stallergenes markets one solution for SLIT as a "named patient product," and the sublingual immunotherapy tablet, Oralair®, that is the subject of this BLA. 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 L.), Orchard (Dactylis glomerata L.), Perennial rye (Lolium perenne L.), Sweet vernal (Anthoxanthum odoratum L.), and Timothy (Phleum pratense L.). All five of these grasses belong to the taxonomic (botanical) family Poaceae (formerly known as Gramineae) and subfamily Pooideae and are among the standardized grasses approved by the FDA for skin-test diagnosis and SCIT.

ORALAIR® is currently marketed throughout the European Union, and has completed Phase 3 testing in the U.S. The applicant proposes the following indication:

"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. Oralair® is approved for use in persons 10 to 65 years of age."

As in Europe, the dosage of the tablets to be used in the U.S. 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 patients 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 biological allergenic units (BAL), the unitage 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 United States).

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 United States have AR.

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

A comprehensive listing of products that are approved to treat AR can be found in the medical officer's review. These include both pharmaceutical drugs (prescription as well as over the counter) and SCIT (subcutaneous injections).

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

There are no allergenic products for grasses licensed or approved for administration in adults or children via SLIT in the U.S. However, several European countries have approved SLIT products for grasses as well as other extracts, including Stallergenes Oralair®.

In 2008, Stallergenes was granted authorization to market Oralair® in Germany. In November 2012, Oralair® was granted European approval for treatment of adults and

children, and is now registered in the following countries: Austria, Belgium, Bulgaria, Cyprus, the Czech Republic, Estonia, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, the Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, and Spain. Also in November 2012, Oralair® was approved in Canada.

In Europe, Oralair® has been studied in five Phase 3 clinical studies in over 1,800 subjects. Most of the studies of this product were performed in Europe and were not submitted to the FDA under an IND prior to their initiation; however, summaries and data from these studies were provided within the BLA submission.

Additional experience can be found in the medical officer's review.

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

Additional information related to the Pre- and Post-submission Regulatory Activity related to this submission can be found in the Medical Officer's and Project Manager's reviews.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

This submission includes the summary of eight (8) pre-marketing efficacy studies and a total of ten (10) pre-marketing safety studies, including approximately 2,500 subjects. Only one large Phase III study was performed under US-IND, while the majority of the remaining studies were not performed under US-IND; however, these studies had similar endpoints and time frames.

3.1 Submission Quality and Completeness

The submission was adequately organized for conducting a complete statistical review without unreasonable difficulty

3.2 Compliance With Good Clinical Practices And Data Integrity

Based on the submitted material and current analysis, it appears the clinical trials were conducted in accordance with acceptable ethical standards.

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

No issues were identified that impacted the statistical review.

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

The BLA submission provided by Stallegenes is located in the following site:
----------(b)(4)----------

This filepath includes the clinical overview, summary of safety, summary of efficacy, as well as datasets for the 8 efficacy studies and 10 safety studies that were examined and analyzed by the reviewing statistician in the review of this product.

The datasets were SAS datasets. A comprehensive "define" document was provided by the applicant and included descriptions of the various datasets as well as variables within each dataset. In addition to the raw data collected from the Case Report Forms (CRFs) and Patient Reported Outcomes (PROs), the applicant also provided derived datasets. These datasets were confirmed by the reviewing statistician, utilizing a variety of methods, including comparisons of PROC FREQ results.

5.1 Review Strategy

The applicant provided summaries and detailed results as well as the datasets of 8 efficacy studies and the 10 safety studies. The primary studies of interest include the Phase III study under US IND (VO61.08USA) as well as the Environmental Exposure Study performed in the EU (VO56.07A). Additionally, studies were examined and select results were confirmed by the reviewing statistician; however, these studies were not performed explicitly under US-IND.

Individual study results are provided in this review for both safety and efficacy results. However, pooled results were also examined, particularly for safety/tolerability and adverse events.

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

The BLA submitted by the applicant is located at the following location:

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

This includes the clinical and non-clinical information, background material, protocol(s), case report forms, and datasets of all studies submitted by the applicant.

The datasets are located in the file paths:

----------(b)(4)----------
(Study VO53.06-Years 1 and 2)
(Study VO61.08USA)

----------(b)(4)----------
(Study VO53.06 Years 3, 4 and 5)

----------(b)(4)----------
(Study VO33.04)
(Study VO34.04)
(Study VO40.05)
(Study VO52.06)
(Study VO56.07A)
(Study VO60.08)

The datasets included both raw data that were imported directly from the case report form (CRF), as well as derived datasets which included (but were not limited to) the total symptom scores, rescue medication scores, and combined symptom scores which incorporated the use of rescue medication and total symptom scores. Additionally the observation of demographic information, safety and adverse events, tolerability endpoints, clinical laboratory values were all included within the datasets provided by the applicant,

5.3 Table of Studies/Clinical Trials

The following table lists a brief summary of the efficacy studies provided within this submission:

Table 5.3.1) Summary of Efficacy Studies including study location, study population, phase of study, dosage, and treatment regimen

Efficacy studies of Oralair®

Study	**Location of the clinical center(s)**	**Population**	**Treatment regimen**	**Dosage examined**
VO34.04	Europe	Adults	A pre- and co-seasonal administration regimen (starting 4 months before the grass pollen season) conducted over a single pollen season	500 IR 300 IR 100 IR
VO61.08USA	USA	Adults	A pre- and co-seasonal administration regimen (starting 4 months before the grass pollen season) conducted over a single pollen season	300 IR
VO56.07A	Europe	Adults	Approximately 4-months, outside the grass pollen season (allergen exposition chamber)	300 IR
VO52.06	Europe	Children and adolescents	A pre- and co-seasonal administration regimen (starting 4 months before the grass pollen season) conducted over a single pollen season	300 IR
VO53.06	Europe, Canada, Russia	Adults	A pre- and co-seasonal administration regimen for three treatment years followed by two immunotherapy-free pollen	300 IR

VO60.08	Europe	Adults and adolescents	A pre- and co-seasonal administration regimen (starting 2 months before the grass pollen season) conducted over a single pollen season	300 IR

Source: Table created by reviewing statistician utilizing data provided in:

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It is important to note that studies VO34.04, VO61.08USA, VO52.06, VO53.06, and VO60.08 were conducted in a natural field environment or natural environmental exposure. All of these studies were single-season studies that examined subject responses for only one allergy season, except VO53.06 which was designed as a four-year study (three treatment years and one treatment-free follow-up year) which was subsequently extended for an additional treatment-free year. Study VO56.07A was conducted in an allergen exposition chamber, outside the grass pollen season.

These studies collected safety data during the entire study period; however, there was one additional study explicitly designed to provide insight into safety/tolerability of this product, V033.034. A summary of the safety studies can be examined in the following table which includes the study number, location, duration of treatment, study design and objectives, subjects exposed and treatment/dosing schedule:

Table 5.3.2) Summary of Oralair® (5-grass pollen extract) sublingual tablet clinical studies and design features

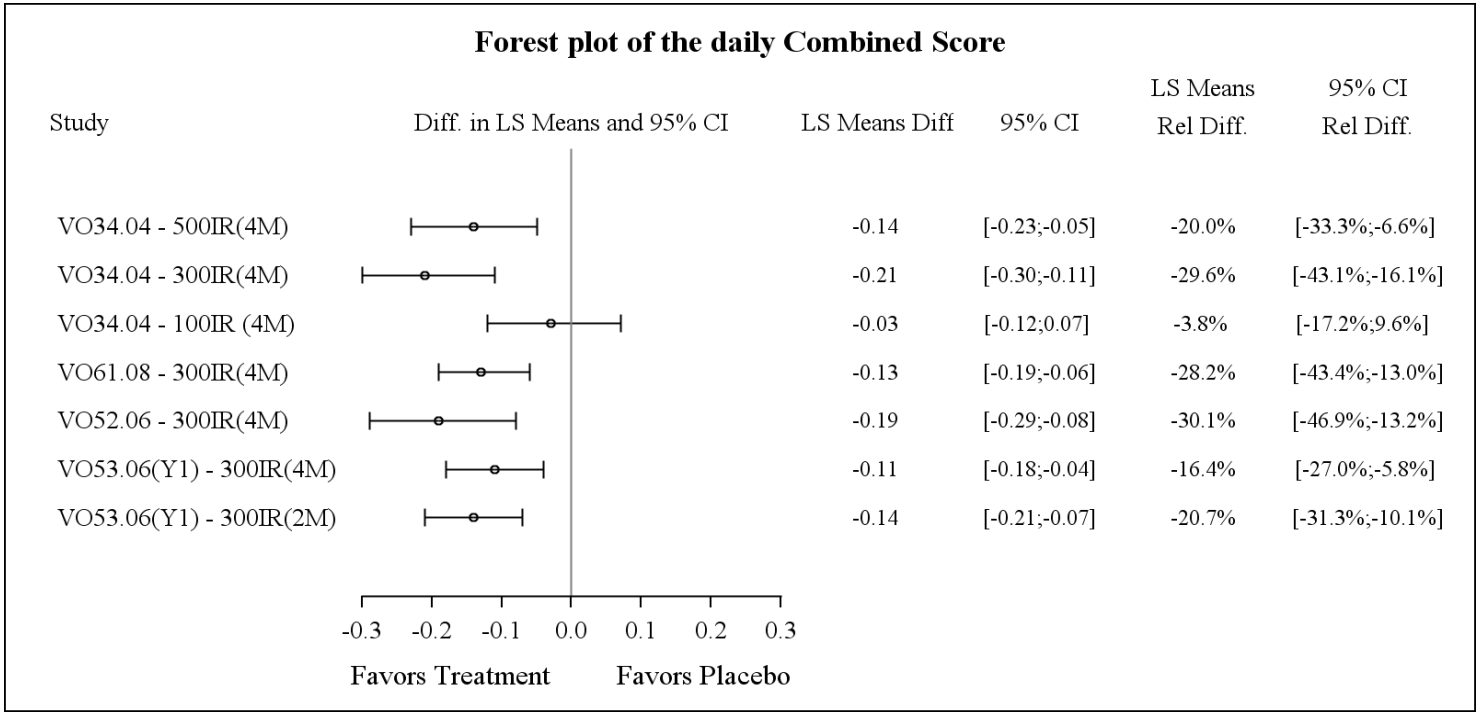
Protocol #	Completion status Year / pollen season	Location	Study title	Study design, & objectives	Study population Age range	Treatment doses & schedule	Number of exposed patients	Treatment duration
VO33.04 DK	Completed 2004 Out of the pollen season	EU	A Phase I/IIa study to investigate the safety, tolerability and pharmacodynamic effects of SLIT given in single rising doses and in higher multi dose regimens.	DBPC, randomized, single center Safety	Adults with grass-pollen allergic rhinitis 18–50	100 IR to 500 IR Placebo Dose escalation or Direct admin	23 7	10 days
VO34.04	Completed 2005	EU	Randomized, double-blind, placebo-controlled, multi-national, multi-centre, Phase IIb/III study of the efficacy and safety of three doses of sublingual immunotherapy (SLIT) administered as tablets once daily to patients suffering from grass pollen rhinoconjunctivitis	DBPC, randomized, multi-national multicenter Efficacy, Safety	Adults with grass pollen- related allergic rhino-conjunctivitis 18–45	500 IR (4M) 300 IR (4M) 100 IR (4M) Placebo Dose escalation	160 155 157 156	~4 months pre-seasonally and ≥ 1 month co-seasonally
VO40.05	Early terminated 2006	EU	A randomized, double-blind, placebo-controlled, multi-national, multi-centre, Phase III extension study to assess the long- term efficacy, safety and carry-over effect of one dose of sublingual immunotherapy (SLIT) administered as allergen-based tablets once daily to patients suffering from grass pollen rhinoconjunctivitis	DBPC, randomized, multi-national multicenter Post-treatment efficacy, Safety (Extension)	Adults with grass pollen- related allergic rhino-conjunctivitis 18-46	300 IR (4M) Placebo Dose escalation	68 25	~4 months pre-seasonally and ≥ 1 month co-seasonally
VO52.06	Completed 2007	EU	A randomized, double-blind, placebo-controlled, multi-national, multi-centre, Phase III paediatric study of the efficacy and safety of 300 IR sublingual immunotherapy (SLIT) administered as allergen-based tablets once daily to children suffering from grass pollen rhinoconjunctivitis	DBPC, randomized, multi-national multicenter Efficacy, Safety	Children and adolescents with grass pollen-related allergic rhino-conjunctivitis 5-17	300 IR (4M) Placebo Dose escalation	139 139	~ 4 months pre- season and ≥ 1 month co

Protocol #	**Completion status** **Year / pollen**	**Location**	**Study title**	**Study design, & objectives**	**Study population** **Age range**	**Treatment doses & schedule**	**Number of exposed patients**	**Treatment duration**
VO53.06	Completed 2007 2008 2009 2010 2011	EU, CAN Russia	A randomized, double-blind, placebo-controlled, multi-national, multi-centre, 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 patients suffering from grass pollen rhinoconjunctivitis	DBPC, randomized, multi-national multicenter Sustained efficacy, Post-treatment efficacy, Safety	Adults with grass pollen- related allergic rhino-conjunctivitis 18-50	300 IR (4M) 300 IR (2M) Placebo Direct administration	207 207 219	4 months pre-seasonally & ≥ 1 month co-seasonally oveears
VO56.07 A	Completed 2007-2008 Out of the pollen season	EU	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	DBPC, randomized, mono-center (allergen exposition chamber study) Efficacy, Safety	Adults with grass pollen- related allergic rhino-conjunctivitis 18-50	300 IR Placebo Direct administration	45 44	4 months
VO60.08	Completed 2009	EU	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 patients suffering from grass pollen rhinoconjunctivitis (with or without asthma)	DBPC, randomized, multi-national multicenter Efficacy, Safety	Adults and adolescents with grass pollen-related allergic rhino-conjunctivitis 12-65	300 IR (2M) Placebo Direct administration	188 193 174	2 months pre-seasonally and ≥ 1 month Co-seasonally
VO61.08 USA	Completed 2009	USA	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 patients suffering from grass pollen rhinoconjunctivitis	DBPC, randomized, multicenter Efficacy, Safety	Adults with grass pollen- related allergic rhino-conjunctivitis 18-65	300 IR (4M) Placebo Direct administration	233 240	4 months pre-seasonally and ≥ 1 month

Source: Original BLA 125471/000; 2.5 Clinical Overview p24-25

A summary of the analysis results based on the Combined Score for the first year of all efficacy studies is provided in Figure 5.3.1 below. This graphic depicts the 95% Confidence interval of the LSMeans comparing the treatment group to the placebo group for the various studies. From the graphic it can be seen that in the majority studies the point estimate of the difference and the 95% CI limits illustrate this product reduces the daily combined score reported by patients.

Figure 5.3.1) 95% Confidence Intervals from Repeated Measures ANCOVA of the Daily CS based on Individual Studies' Models and on Individual Databases



Source: Original BLA 125471/000; 2.5 Clinical Overview p29
Primary analysis set of studies V studies VO34.04, VO61.08USA, and VO52.06 and primary analysis set Year 1 of study VO53.06

For completeness, the results of all study arms are included in the Figure (although of primary interest in this BLA is 300IR(4M)). Although this graph is provided by the applicant, the reviewing statistician was able to confirm the LSMeans, 95% CI of the LSMeans, LSMeans Relative Difference, and 95% of the Relative Difference via ANCOVA utilizing Proc Mixed within SAS.

5.4 Consultations

5.4.1 Advisory Committee Meeting

An Advisory Committee Meeting was held on December 11, 2013 to discuss this product and associated clinical studies.

5.4.2 External Consults/Collaborations

n/a

5.5 Literature Reviewed

Within this submission the applicant provides several articles related to the studies performed. These articles have extensive references, of which the statistician utilized several journal articles as well as websites (in particular World Allergy Organization-WAO published suggested standards).

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

This submission included the results of six randomized, double-blind, placebo-controlled clinical trials to examine the safety/tolerability and efficacy of Oralair®:

- VO34.04 (European study-in Adults),
- VO61.08US (US study-in Adults),
- VO56.07A (Allergen exposure chamber study-in Adults),
- VO52.06 (Pediatric study-in Adolescents and Children),
- VO53.06 (Long Term study-in Adults), and
- VO60.08 (Alternate regimen study-in Adults, Adolescents and Children)

Additionally, the applicant examined the safety/tolerability of this product in two additional adult studies: VO33.04DK (N=30) and VO40.05 (an extension of study VO34.04).

The studies of primary interest in the examination of the efficacy of this product, Oralair®, are the Phase III study performed under US-IND and the environmental chamber study performed in the EU:

- VO61.08US (US study-in Adults),
- VO56.07A (Allergen exposure chamber study-in Adults),

Key design features for the studies that were consistent among all studies include the following.

Randomization
In all studies, patients who fulfilled all the inclusion criteria and none of the exclusion criteria were randomized to active therapy or placebo, with a treatment assignment ratio (or allocation ratio) leading to groups of equal size (ratio 1:1, 1:1:1, 1:1:1:1 for studies with placebo and one, two, or three active treatment groups, respectively). A computer-generated randomization list was prepared for each study. Block design was used to create balance in the treatment assignments over time as recruitment progressed (blocks of 4 for the 1:1 and 1:1:1:1 ratio, and blocks of 6 for the 1:1:1 ratio). All multicenter studies were stratified by study center, by allocating complete blocks to each center.

Control treatment
The efficacy studies were placebo-controlled.

The placebo tablets appeared identical to the active treatment tablets with respect to physical characteristics (i.e., color, weight, taste, size, and shape), the number of tablets per treatment box, and the number of tablets to be taken daily. The excipients were also the same as those used in the active treatment tablets.

Blinding
All studies addressed in this document were double-blind.

The issue of blinding specific immunotherapy studies is raised in the Food and Drug Administration's (FDA) *Guidance for Industry: Allergic Rhinitis, Clinical Development Programs for Drug Products* (April 2000) and in the EMA Guideline [EMA, 2008]: "superiority versus placebo or any other comparator has to be shown. Since local allergic adverse events are frequent in specific immunotherapy, a placebo preparation with histamine may be considered to keep the blinding."

Treatment Schedules
The various study treatment schedules were not consistent among all studies. Thus, discussions related to the treatment schedule will be further detailed within the individual studies. Overall, the applicant administered treatment well in advance of the anticipated pollen season (16 weeks) throughout the entire pollen season or prior to the environmental chamber study. After the season (or chamber study) was completed treatment was discontinued. In one study, administration of treatment occurred for several pollen seasons with discontinuation immediately following the pollen season.

Patient population
The patients enrolled in the clinical development program were representative of the population consulting allergy practices for treatment of grass pollen-related allergic rhinoconjunctivitis. Through a variety of mechanisms patients with allergies to grass pollens were to be identified and those meeting eligibility criteria and agreeable to study participation were to be enrolled and randomized.

Choice and description of study endpoints
The clinical development program of Oralair® sublingual tablet began by Stallergenes in 2004. Throughout the program, the applicant has designed its studies in line with

appropriate health authority guidelines, including the US-FDA, with respect to the single study performed under US-IND. The other field exposure studies had similar endpoints and time frames, while the environmental exposure study had similar endpoints but the time frame was limited to several hours within the exposure chamber.

The primary efficacy endpoints for the efficacy clinical program varied slightly for several of the studies; however, generally the endpoints, timing of administration, and data collection were similar. Specifically, at the time the European trial (VO34.04), Pediatric trial (VO52.06), and Long Term trial (VO53.06) were set up, the guidelines on the clinical development of new products for the treatment of allergic rhinitis recommended, as the primary variable, a total score of rhinitis and conjunctivitis symptoms with each symptom being assessed on a 4-point scale from 0 (no symptom) to 3 (severe symptom). While studies VO34.04 and VO52.06 were already completed, study VO53.06 was ongoing and the study protocol was amended in the second year to opt for a primary endpoint reflecting both measures [protocol amendment 02, 11 December 2008]. In study VO61.08USA, the US study, the primary variable is the daily Combined Score, composed of the symptom score (50%) and the rescue medication score (50%).

Symptoms scores and medication use were recorded daily by the patient on a daily record card:

Symptoms were graded by patients on a 0–3 scale:

- 0 = Absent symptoms (no sign/symptom evident).
- 1 = Mild symptoms (sign/symptom clearly present, but minimal awareness; easily tolerated).
- 2 = Moderate symptoms (definite awareness of sign/symptom that is bothersome but tolerable).
- 3 = Severe symptoms (sign/symptom that is hard to tolerate; causes interference with activities of daily living and/or sleeping).

The daily Rhinoconjunctivitis Total Symptom Score (RTSS) was the total of the six daily symptom scores for each day (sneezing, rhinorrhea, nasal pruritus, nasal congestion, ocular pruritus, and watery eyes) for each patient, resulting in a scale of 0 to 18.

In natural field studies, in order to manage severe rhinoconjunctivitis symptoms, patients were permitted to take rescue medication according to a stepwise regimen described in each protocol. The daily Rescue Medication Score (RMS) was defined by Stallergenes based on the hypothesis that a nasal corticosteroid is more efficient than an antihistamine and an oral corticosteroid is more efficient than a nasal corticosteroid, leading to a derived ordinal score: 0=absent, 1=antihistamine, 2=nasal corticosteroid, 3=oral corticosteroid. In case the patient took two or more rescue medications, the higher score was retained for the corresponding day. Methodologically, this approach with no additional assumptions regarding the weighting of each rescue medication dose or the additive effect of different rescue medications enhances the robustness of the scale.

The daily Combined Score (CS) is a score taking into account the RTSS and RMS and assuming equivalent importance of symptoms and medications score. This score is

conventionally expressed on a scale from 0 to 3 and calculated for each day for each patient as:

Daily CS = (daily RTSS / 6 + daily RMS) / 2.

The patient evaluates his/her symptom score retrospectively over the previous 24 hours. When (s)he takes a rescue medication, the symptom score assessment on the day of intake and on the following day may be impacted. Therefore, the symptom score is adjusted accordingly. Both ASS and AASS range from 0 to 18.

General Statistical approach

For each study in the clinical development program, all analyses were pre-specified in the respective protocol and detailed in the associated Statistical Analysis Plan (SAP) and its amendments. Each SAP also described the models to be used for the endpoint analyses, validity assumptions, handling of missing data, and how potential statistical issues were to be addressed.

The statistical approach used to analyze the efficacy endpoints and present the results was consistent throughout the clinical development program. The size of the studies allowed the use of parametric models. In all studies, the primary efficacy endpoint [i.e., the symptom score or symptom/rescue medication score, (dependent variable)], was analyzed using a linear model, specifically an ANCOVA with treatment as main effect, pooled study center as stratification factor for the multicenter studies, and several covariates which could potentially impact the clinical score. (ANCOVA is a statistical model for comparing means of independent groups while controlling for covariates.)

As a result of the nature of the variable (i.e., all recorded values during the pollen season vs. a summary measure), the approach specified for the primary analysis of the study VO61.08USA daily Combined Score was a repeated measures ANCOVA model and in the other studies, an ANCOVA of the average of the daily symptom scores over the evaluation period, either unadjusted for rescue medication use (ARTSS, studies VO34.04, VO56.07A and VO52.06) or adjusted for it (AASS, studies VO53.06 and VO60.08), was used. For study VO61.08USA, a SAS MIXED procedure with repeated measures was run, and for the latter studies the model was fitted with the SAS Generalized Linear Model (GLM) procedure. For study VO56.07A, a SAS MIXED procedure was run.

Analysis sets

In each natural field study, consistent with the ICH E9 Guideline (Statistical Principles for Clinical Trials) to "describe the analysis set which is as complete as possible and as close as possible to the Intention-To-Treat ideal of including all randomized subjects," the primary efficacy analysis included data from all patients who received at least one dose of the investigational product and had recorded the primary efficacy measure on at least one day during the pollen period while on treatment. For this reason, according to the ICH E9 Guideline, each primary analysis set is termed "Full Analysis Set" (FAS).

6.1 **Trial #1: VO61.08US-US Phase III Study**

Stallergenes trial VO61.08US was submitted to the Agency under US-IND to be "*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 patients suffering from grass pollen rhinoconjunctivitis.*"

6.1.1 Objectives (Primary, Secondary, etc.)

The objectives of this study were to evaluate the efficacy and safety of sublingual tablets of grass pollen allergen extract compared with placebo for reduction of rhinoconjunctivitis symptoms and rescue medication usage.

Primary efficacy objective:

To assess the efficacy of sublingual tablets of grass pollen allergen extract during the pollen period on:

- The daily Combined Score (CS): A score taking into account the Rhinoconjunctivitis Total Symptom Score (RTSS) and the Rescue Medication Score (RMS).

6.1.2 Design Overview

This was a randomized, double-blind, placebo-controlled, multi-center, phase III study with two parallel arms in patients with grass pollen-related allergic rhinoconjunctivitis.

Eligible male or female patients were to be randomized approximately 4 months before the expected start of the grass pollen season to one of two treatment groups (either 300 index of reactivity [IR] tablet of grass pollen allergen extract or placebo). Each treatment group was to comprise approximately 212 randomized patients. Patients in both treatment groups were asked to take the investigational product tablets sublingually once daily, at the same time, for approximately 6 months.

The study consisted of a:

- Screening Phase (1 to 12 weeks),
- Treatment Phase (approximately 6 months) and
- Follow-up Phase (2 weeks).

Reviewer Comment: The study as proposed and implemented was acceptable to the statistical reviewer. Initially, the Agency had suggested a different and more stringent threshold for the upper boundary for the 95% confidence interval; however, based upon feedback from many applicants and discussions held during the May 2011 APAC it was determined that a -10% margin for the upper bound of the 95% CI was sufficient. This revised upper bound threshold was agreeable to the Agency, and it was utilized as the standard criteria for efficacy for all field studies for seasonal allergies caused by grass pollens.

6.1.3 Population

The treatment population consisted of male or female patients aged 18 to 65 years (inclusive) with documented grass pollen-related allergic rhinoconjunctivitis for at least

the last two pollen seasons, a positive SPT to Timothy grass (longest diameter of flare ≥ 10 mm and wheal diameter ≥ 5 mm, greater than the negative control), a score of ≥ 12 (scale 0 to 18) on the Retrospective Rhinoconjunctivitis Total Symptom Score (RRTSS) for the previous grass pollen season, and FEV1 ≥ 80% of the predicted value. Patients were not to be symptomatic to any other allergen present during the grass pollen season and were not to have a positive SPT to any other grass allergens present during the grass pollen season including Bermuda, Bahia, and Johnson grass (if these grasses were endemic to the region).

6.1.4 Study Treatments or Agents Mandated by the Protocol

In this study, two treatments were to be examined and compared: Oralair® 300IR tablets and Placebo tablets that matched the 300IR Oralair® tablets. Both the active treatment and placebo were to be administered sublingually (under the tongue) every day at the same time during the approximate 6-month treatment period.

6.1.6 Sites and Centers

This study was to include 51 study centers in various locations with expected exposure to grass pollen in the US.

6.1.7 Surveillance/Monitoring

The surveillance and monitoring of the study can be found in the clinical reviewer's and epidemiologist's reviews.

6.1.8 Endpoints and Criteria for Study Success

There are several primary and secondary endpoints in this study that were utilized to assess how well the Oralair® product reduced symptoms related to grass allergies, as well as reduced the need to take medications to treat or prevent symptoms associated with grass allergies. The primary criterion for success was the combined symptom score (CS), which consisted of the patient's daily rhinoconjunctivitis symptom scores (RTSS) and rescue medication scores (RMS).

<u>Primary efficacy variable</u>:
The daily combined symptom score (CS) is a daily patient-specific score taking into account the patient's daily rhinoconjunctivitis symptom scores (RTSS) and rescue medication scores (RMS), assuming equivalent importance of symptoms and medication scores.

The CS score is calculated as: CS = (RTSS / 6 + RMS) / 2

<u>Secondary efficacy variables</u>:

- Adjusted Symptom Score (ASS): The daily ASS is an adjusted RTSS based on the patient's rescue medication usage. It is patient-specific and takes into account that patients were allowed to make use of any of the three categories of rescue medication.

- Rhinoconjunctivitis Total Symptom Scores (RTSS): The daily RTSS is the sum of the six (non-missing) rhinoconjunctivitis symptom scores as evaluated by the patient using a score from 0 to 3.
- Rescue Medication Score (RMS): The daily RMS was assigned daily to the different medications used as rescue medication.
- Rhinoconjunctivitis symptoms (RSS): The severity of each of the six individual rhinoconjunctivitis symptoms was scored daily.

In addition, each daily (non-missing) variable CS, ASS, RTSS, RMS, and RSS was summarized as the Average CS (ACS), ASS (AASS), RTSS (ARTSS), RMS (ARMS), and RSS (ARSS) during the pollen period/worst pollen period while the patient was on treatment. [Some intro to the list below is needed.]

- The proportion of patients who used rescue medication during the pollen period and worst pollen period while on treatment.
- The proportion of days rescue medication was used during the pollen period and worst pollen period while on treatment.
- Proportion of Symptom-Controlled Days (PSCD).
- Controlled patients (CP).
- Overall Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) score.
- Global evaluation of the efficacy of the treatment by the patient.
- Sensitization status (mono-/poly-sensitized) derived from the SPT.
- Asthma status and severity. Other variables:[Where are they?]
- The proportion of valid CS days during the pollen period and worst pollen period while on treatment.
- Immunological markers (IgE and IgG4 specific for timothy grass pollen allergen).
- SPT results.
- Economic evaluation.

Safety variables:

- Adverse events (AEs).
  - Laboratory assessments.
  - Physical examinations.
  - Vital signs.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Analysis sets:

For the purpose of this study, three analysis sets were defined, namely, the Safety Set, the Full Analysis Set (FAS), and the Per Protocol Analysis Set (PPS), which were pre-specified and defined as follows:

- The Safety Set includes all patients who received at least one dose of the investigational product.
- The FAS includes all patients who received at least one dose of investigational product and had at least one CS while on treatment during the pollen period. The FAS was regarded as the primary population for the efficacy analyses.

- The PPS includes all patients from the FAS who had at least 14 days of valid CS during the pollen period while on treatment and who completed the study according to the protocol and had no major protocol deviations.

Efficacy analyses:

The primary efficacy endpoint was the daily Combined Score (CS) during the pollen period while on treatment. Secondary endpoints included the Average Combined Score (ACS), the daily Adjusted Symptom Score (ASS), and the Average Adjusted Symptom Score (AASS), the daily Rhinoconjunctivitis Total Symptom Score (RTSS), and the Average Rhinoconjunctivitis Total Symptom Score (ARTSS), the daily Rescue Medication Score (RMS), the Average Rescue Medication Score (ARMS), the overall Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) score, and the global evaluation of treatment efficacy by the patient. Several additional secondary efficacy endpoints as well as several safety/tolerability analyses were also planned and implemented.

Determination of sample size:

At the time of the protocol submission to the FDA, the applicant proposed that the primary endpoint of interest was AASS, and based on this the sample size was calculated as described below.

With an alpha of 0.05, a two-sided test and a common SD of 3.603 (as observed in a previous phase I/II study entitled, VO34.04 which was presented in this BLA submission), a sample size of 191 patients per treatment group would provide 90% power to detect a mean difference of -1.2 between placebo and 300 IR in the AASS during the pollen period during treatment.

Assuming a drop-out rate of 10%, it was planned to randomize 424 patients in order to have 212 patients in each treatment group at the start of the study. Assuming a screening failure rate of 20%, it was planned to screen approximately 550 patients.

Subsequently, upon FDA's recommendation, the primary endpoint was changed to the daily Combined Score (CS). The expected mean difference in the CS between the 300 IR group and the Placebo group was defined as -0.14 with a proposed common SD of 0.50.

Given an alpha of 0.05, a common SD of 0.50, a two-sided test and at least 202 evaluable patients per treatment group, the study had a power of at least 80% to detect a mean difference between treatments of -0.14 based on daily combined symptom scores noted during the entire pollen period.

Reviewer Comment: *The study endpoint and threshold for a clinically meaningful difference was modified based on mutual agreement between the Agency and applicant. These adjustments were in response to feedback provided and issues discussed during the May 2011 APAC meeting. The proposed modifications are acceptable and reasonable.*

6.1.10 Study Population and Disposition

The study population and baseline demographics of the enrolled patients are similar for both treatment groups. In this study, 473 patients were randomized to treatment.

6.1.10.1 Populations Enrolled/Analyzed

The following table illustrates the study population distribution in study VO61.08USA.

Table 6.1.10.1.1 Summary of Patient Population

	Treatment 300 IR N (%)	Treatment Placebo N (%)	Total N (%)
Patients Randomized	233 (100%)	240 (100%)	473 (100%)
Patients in Safety Set	233(100%)	240 (100%)	473 (100%)
Patients in Primary/Full Analysis Set	210 (90%)	228 (95%)	438 (92.6%)

Source: Table created by reviewing statistician utilizing data provided in:

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

6.1.10.1.1 Demographics

The demographics of the individuals included in this study can be seen in the following table. Within the table the number of individuals and percent of individuals is noted for each treatment group based on the demographic variables of gender, age and race. This table illustrates that the baseline characteristics were similar for both treatment groups.

Table 6.1.10.1.1 Baseline Demographics of the Patient Population

Baseline Demographic	Treatment Group 300 IR N=210	Treatment Group Placebo N=228	**Total N=438**
Gender [n (%)]			
Female	109 (51.9)	125 (54.8)	234 (53.4)
Male	101 (48.1)	103 (45.2)	204 (46.6)
Age (years)			
Range	18 – 65	18 – 65	18 – 65
Race [n (%)]			
White/Caucasian	188 (89.5)	207 (90.8)	395 (90.2)
Black or African American	12 (5.7)	15 (6.6)	27 (6.2)
Asian	5 (2.4)	0 (0.0)	5 (1.1)
American Indian/Alaska Native/Pacific Islander	0 (0.0)	2 (0.9)	2 (0.5)
Other	5 (2.4)	4 (1.8)	9 (2.1)

Source: Table created by reviewing statistician utilizing data provided in:

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6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

The medical/behavioral characteristics of the individuals included in this study can be seen in the following table. Within the table the mean and standard deviation of various relevant medical/behavorial characteristics is noted for each treatment group based on the BMI, asthma status and sensitivity to allergens (mono versus polysensitized). This table illustrates that these characteristics were similar for both treatment groups.

Table 6.1.10.1.2 Baseline Medical/Behavioral Characteristics of the Patient Population

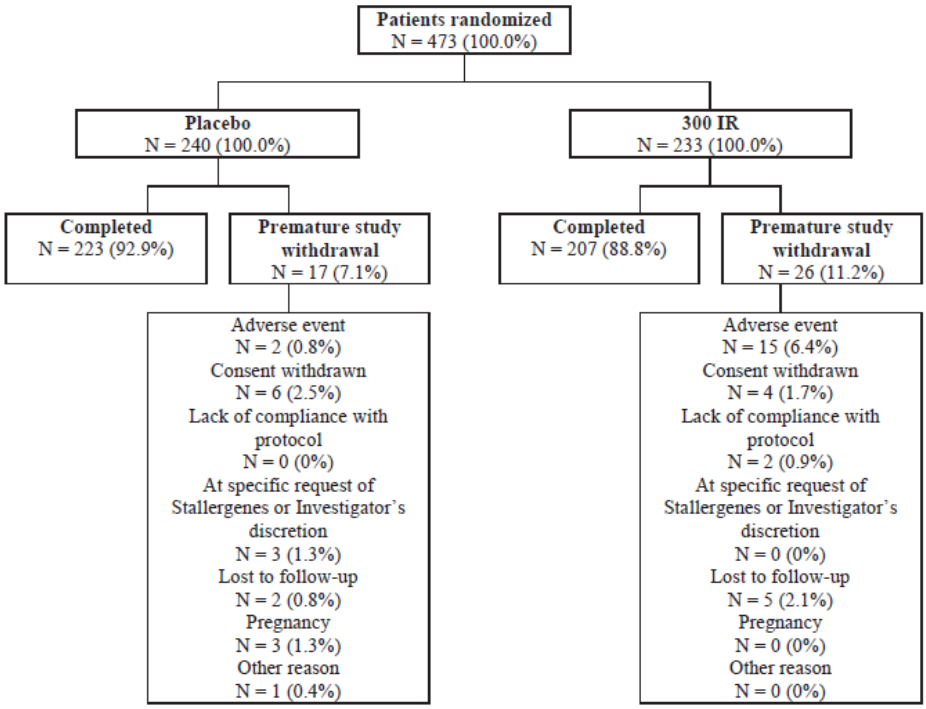
Baseline Demographic	Treatment Group **300 IR N=210**	Treatment Group **Placebo N=228**	**Total N=438**
BMI (kg/m²)			
Mean (SD)	27.8 (5.83)	28.5 (5.75)	28.2 (5.80)
Range	16.7 – 48.8	17.3 – 50.7	16.7 – 50.7
Asthma Status [n (%)]			
Presence	38 (18.3)	50 (21.9)	88 (20.2)
Absence	170 (81.7)	178 (78.1)	348 (79.8)
Sens.stat. [n (%)]			
Mono-sensitized	44 (21.0)	53 (23.2)	97 (22.1)
Poly-sensitized	166 (79.0)	175 (76.8)	341 (77.9)

Source: Table created by reviewing statistician utilizing data provided in:
----------(b)(4)----------

6.1.10.1.3 Subject Disposition

The following figure illustrates the randomization, allocation, and withdrawal of patients for this study. This graphic notes which treatment arm subjects were randomized to and subsequently lists the reason for dropout including the number of subjects and percentage of subjects that withdrew prior to study completion. It is of interest to note the adverse event rate is slightly higher in the active treatment group; however, other reasons for dropout were fairly similar between the placebo and treatment groups.

Figure 6.1.10.1.3.1 Patient Disposition



Source: Original BLA 125471/000; Clinical Study Report VO61.08 p81

6.1.11 Efficacy Analyses

The applicant proposed and implemented the following efficacy analyses within this study.

Primary efficacy analysis:
The primary efficacy endpoint, the daily CS during the pollen period while on treatment in the FAS, was analyzed using a repeated measures analysis of covariance (ANCOVA) model. This model included treatment group and the count of valid CSs by patient as fixed effects; patient identifier as random effect and pooled study center, age, gender, asthma status (Yes/No), and sensitization status (mono-/poly-sensitized) as covariates. This model provided adjusted Least-Square means (LS means) estimates along with the difference versus placebo of these estimates, the corresponding 95% confidence interval (CI), and the p-value.

Secondary efficacy analyses:
The primary analysis was repeated for the PPS on the primary efficacy endpoint.

Additional analyses performed:
- Daily CS during the worst pollen period in the FAS and PPS
- ACS using an ANCOVA model during the pollen period and the worst pollen period in the FAS and PPS.
- Daily CS and ACS in 4 subgroups depending on patients' Timothy-grass IgE level at inclusion (< 0.1, < 0.7, ≥ 0.1, ≥ 0.7 kU/L) in the FAS.

The daily ASS and daily RTSS were analyzed in the same way as per the daily CS and the AASS and ARTSS as per the ACS, during the pollen period and worst pollen period in the FAS and PPS for all these variables.

The daily RMS and six individual RSSs, as well as ARMS and ARSSs, were analyzed using the same methodological approaches as described above for the primary endpoints during the pollen period and worst pollen period in the FAS only.

Other analyses:
The following variables were summarized descriptively:

- Proportion of valid CS days during the pollen period and worst pollen period in the FAS and PPS.
- The Proportion of Symptom-Controlled Days (PSCD) (%) during the pollen period and worst pollen period in the FAS and PPS.
- The overall score of the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) during the pollen period and worst pollen period in the FAS and PPS were summarized by treatment group.
- The sensitization status, asthma status, and asthma evaluation were summarized descriptively by treatment group
- The levels of immunological markers at baseline, Visit 5 and Visit 6 with Visit 5/baseline and Visit 6/baseline ratios.
- The Skin Prick Test (SPT) results specific for grass pollen and for other allergens using shift tables from Visit 1 to Endpoint that compute the differences in the SPT over time.
- The proportion of days off work/studies/daily activities (%) due to grass pollen-related rhinoconjunctivitis at Visit 5 and Visit 6.

6.1.11.1 Analyses of Primary Endpoint(s)

The primary efficacy endpoint is the daily Combined Score (CS) during the pollen period while on treatment. The primary analysis was performed for the Full Analysis Set (FAS), which included all patients who received at least one dose of the investigational product.

The daily CS was analyzed using a repeated measures ANCOVA model, with treatment group and count of valid CSs by patient as fixed effects; patient identifier as random effect; and pooled study center, age, gender, asthma status (Yes/No), and sensitization status (mono-/poly-sensitized) as covariates. A decrease in the score represents an improvement.

The repeated measures ANCOVA model results for the primary efficacy analysis of the daily CS during the pollen period for the FAS are summarized below. The point estimate is the LS Mean difference between 300 IR and placebo, and the relative LS Mean difference is equal to (LS Mean difference/LS Mean for the Placebo group) x 100.

For the tables provided in this review the calculations were performed utilizing SAS Proc MIXED with the model noted within the footnotes as well as the variance/covariance

structure utilized. If additional methods were utilized to compute the 95% CI to verify and confirm the robustness of results, the methods are noted in the table footnotes.

The mixed model is a combination of fixed and random effects parameters and is written as follows:

$$\mathbf{y=X\beta+Z\gamma+\varepsilon}$$

where y denotes the vector of observed y_{ij}'s, X is the known matrix of x_{ij}'s, β is the unknown fixed effects parameter vector. Z is the known design matrix of z_{ij}'s, γ is the vector of unknown random effects parameters and, ε is the unobserved vector of independent and identically distributed Gaussian random errors.

The results in the first column of this table provide the estimate of the mixed model including the linear estimate for the contrast vector (L) and the approximate standard error for the LS-Mean (computed as the square root of $L(X'V^{-1}X)^{-1}L'$, where V is the variance/covariance structure).

As an additional method to ensure robustness of results, the reviewing Agency statistician utilized the delta method to estimate the 95% CI of the difference between the treatment and placebo group. These results, which can be seen in the below table, confirmed the applicant's results and provided an additional analysis supporting the applicant's conjecture that this product reduces the combined symptom and rescue medication score when compared to placebo.

Table 6.1.11.1.a. Primary Efficacy Analysis: Repeated Measures ANCOVA of the Daily CS during the Pollen Period – FAS[1]

Treatment	n	LS Mean	LS Mean difference vs Placebo Point Est	LS Mean difference vs Placebo 95% CI	Relative LS Mean difference (%) Point Est	Relative LS Mean difference (%) 95% CI	*Relative LS Mean difference (%)* *Point Est*	*Relative LS Mean difference (%)* *95% CI (using the delta method)*
300 IR	208	0.3202	-0.13	[-0.19, -0.06]	-28.2%	[-43.4%, -13.0%]	*-28.2%*	*[-46.1%, -10.4%]*
Placebo	228	0.4462						

Source: Table created by reviewing statistician utilizing data provided in:

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[1] N=number of Patients in FAS.Model utilized: ANCOVA with patient/subject ID, pooled (geographically) center, age, gender, asthma status, and sensitization status. SAS: PROC MIXED with repeated effect based on Subject and Compound Symmetry as Var/Cov structure. As an additional analysis method, the delta method was used to calculate the confidence intervals.

The difference in LS means of the daily CS during the pollen period between the 300 IR group and the Placebo group was statistically significant. The treatment effect was estimated as the difference in LS means of -0.126, corresponding to a relative LS Mean difference of -28.2% from placebo. The 95% CI expressed as percentages was [-43.4%,

-13.0%]. Furthermore, utilizing the delta method, the 95% CI expressed as percentages was [-46.1%, -10.4%], which satisfies the Agency suggested pre-specified criterion of meeting a 10% threshold for reduction of combined symptom scores.

6.1.11.2 Analyses of Secondary Endpoints

In addition to the primary endpoint of interest, the combined symptom and rescue medication score, several secondary endpoints were of interest. These include but are not limited to the combined scores during the worse pollen season, as well as the symptom scored use of rescue medication, and analysis of the data during both the pre-specified pollen season as well as "worst pollen period."

During the worst pollen period, the difference in LS means of the daily CS was statistically significant between the 300 IR group and the Placebo group. The treatment effect was estimated as the difference in LS means of -0.126, corresponding to a relative LS Mean difference of -24.2% from placebo. The model did not converge regardless of var/cov structure or method utilized to estimate the confidence interval; thus, the 95% CI that were computed via SAS and presented below should be interpreted with caution.

Table 6.1.11.2.a. Primary Efficacy Analysis: Repeated Measures ANCOVA of the Daily CS during the Worst Pollen Period – FAS[1]

Treatment	n[1]	LS Mean	LS Mean difference vs Placebo Point Est	LS Mean difference vs Placebo 95% CI	Relative LS Mean difference (%) Point Est	Relative LS Mean difference (%) 95% CI
300 IR	208	0.39	-0.13	[-0.21, -0.05]	-24.4%	[-44.1%, -4.6%]
Placebo	228	0.52				

Source: Table created by reviewing statistician utilizing data provided in:
----------(b)(4)----------

[1] n=number of Patients in FAS
Model utilized: ANCOVA with patient/subject ID, pooled (geographically) center, age, gender, asthma status and sensitization status. SAS: PROC MIXED with repeated effect based on Subject and Compound Symmetry (CS) as Var/Cov structure.

Similar trends, in which the point estimate illustrates that the placebo does not reduce symptoms to the extent that the treatment does, can be observed for both the full analysis set as well as the per protocol analysis set for the combined score as well as the symptom score.

Additionally, examining the use of rescue medication illustrates that the use of medication decreased in the treated group versus the placebo group. The difference in LS means of the daily RMS during the pollen period between the two groups, LS Mean difference of -46.5% versus placebo, can be seen below in Table 6.1.11.2.b.

Table 6.1.11.2.b. Primary Efficacy Analysis: Repeated Measures ANCOVA of the Daily Rescue Medication S during the Worst Pollen Period – FAS[1]

Treatment	n[1]	LS Mean	LS Mean difference vs Placebo Point Est	LS Mean difference vs Placebo 95% CI	Relative LS Mean difference (%) Point Est	Relative LS Mean difference (%) 95% CI
300 IR	208	0.11	-0.09	[-0.15, -0.04]	-46.5%	[-76.1%, -16.7%]
Placebo	228	0.20				

Source: Table created by reviewing statistician utilizing data provided in:
----------(b)(4)----------
[1] n=number of Patients in FAS
Model utilized: ANCOVA with patient/subject ID, pooled (geographically) center, age, gender, asthma status and sensitization status. SAS: PROC MIXED with repeated effect based on Subject and Compound Symmetry as Var/Cov structure.

Table 6.1.11.2.c. Primary Efficacy Analysis: Repeated Measures ANCOVA of the Rescue Medication Use during the Pollen Period – FAS

Treatment	n[1]	LS Mean	LS Mean difference vs Placebo Point Est	LS Mean difference vs Placebo 95% CI	Relative LSMean difference (%) Point Est
300 IR	208	0.14	-0.10	[-0.15, -0.04]	-40.5%
Placebo	228	0.24			

Source: Table created by reviewing statistician utilizing data provided in:
----------(b)(4)----------
[1] n=number of Patients in FAS

Model utilized: ANCOVA with patient/subject ID, pooled (geographically) center, age, gender, asthma status and sensitization status. SAS: PROC MIXED with repeated effect based on Subject and Compound Symmetry as Var/Cov structure

The following illustrates the difference between the placebo and treatment groups. Within this table the symptom class, sample size in each treatment arm, point estimate of the LSMean per treatment arm as well as LSMean difference, 95% CI of the LSMean and relative LSMean Difference. This is a secondary analysis in which the study was not powered to detect differences between treatment groups nor were alpha adjustments made for these hypothesis tests; however, the trends observed within the table indicate that the treatment reduces the specific symptoms when compared to individuals randomized to the placebo treated group.

Table 6.1.11.2.c Secondary Efficacy Analysis: Repeated Measures ANCOVA of the Individual Daily RSS during the Pollen Period – FAS

Treatment	n[1]	LS Mean	LS Mean difference vs Placebo Point Est	LS Mean difference vs Placebo 95% CI	Relative LS Mean Difference (%)
Sneezing					
300 IR	208	0.65	-0.15	[-0.27, -0.03]	-18.7
Placebo	228	0.80			
Runny Nose					
300 IR	208	0.57	-0.15	[-0.27, -0.02]	-20.6
Placebo	228	0.72			
Itchy Nose					
300 IR	208	0.49	-0.11	[-0.23, 0.02]	-17.6
Placebo	228	0.59			
Nasal Congestion					
300 IR	208	0.71	-0.15	[-0.28, -0.01]	-17.4
Placebo	228	0.85			
Itchy Eyes					
300 IR	208	0.48	-0.22	[-0.35, -0.09]	-31.2
Placebo	228	0.70			
Watery Eyes					
300 IR	208	0.31	-0.18	[-0.29, -0.07]	-37.1
Placebo	228	0.49			

Source: Table created by reviewing statistician utilizing data provided in:
----------(b)(4)----------
[1] n=number of Patients in FAS
Model utilized: ANCOVA with patient/subject ID, pooled (geographically) center, age, gender, asthma status and sensitization status. SAS: PROC MIXED with repeated effect based on Subject and Compound Symmetry as Var/Cov structure.

6.1.11.3 Subpopulation Analyses

Several subpopulations were of interest to the medical officer: IgG, IgE, and asthma status. Additionally, based on current regulations, there should be analyses based on gender, age, and race. In this study, more than 95% of the enrolled subjects were caucasian/white and the study examined patients 18-50 years of age; thus, subgroup analysis of the primary endpoint based on race and age is not informative. However, a comparison of the male vs female outcomes was performed by the Agency Statistician.

Table 6.1.11.3 Comparison of Average Combined Score Stratified by Gender

Treatment	Male (n=204) n	Male (n=204) Mean CS	Female (n=234) n	Female (n=234) Mean CS
300 IR	101	0.33	109	0.42
Placebo	103	0.50	125	0.50

Source: Table created by reviewing statistician utilizing data provided in:
----------(b)(4)----------

From the above table, it can be seen that there is an observable positive treatment effect for both male and female subjects, but the effect appears to be slightly greater among males.

6.1.11.4 Dropouts and/or Discontinuations

As per the applicant, some subjects were excluded from the primary analysis due to lack of daily CS data during the pollen period while on treatment. For example, the applicant suggested that subjects withdrawn before the start of the pollen period or subjects with missing daily record card data would be excluded from analysis. These drop-outs were accounted for in the sample size calculations. It was noted in the protocol that 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 comment: *The proposed treatment of exclusions and missing values was acceptable. Comparisons of missing value rates were made and were deemed comparable for both treatment groups. Additional sensitivity analyses, imputing missing values utilizing LOCF, worst case scenario (i.e., assigning maximum value for missing values), and best case scenario (i.e., assigning minimum value for missing values), yielded similar results.*

6.1.11.5 Exploratory and Post Hoc Analyses

The applicant provided a variety of exploratory and post hoc analyses. These analyses included but were not limited to comparisons of combined score, rescue medication score, symptom scores for IgG4, IgE, as well as examination of secondary endpoint analysis over peak and entire pollen season. A variety of these analyses were confirmed by the reviewing statistician. The analysis of the IgG4 and IgE scores appeared to be positively affected by the use of the active treatment when compared to placebo treated individuals however; there was a large amount of variability. Additionally, analysis of select endpoints, time frames and analysis sets illustrated that the trends observed in which the active treatment reduced the use of rescue medication, and reduced the severity

based on symptom scores of a variety of nasal and oral endpoints. This was consistent for the full pollen season as well as the worst pollen season and for different analysis sets that were available

6.1.12 Safety Analyses

Safety data were collected for the entire study period. Subjects were able to note safety events on the daily diary cards, and also received periodic follow-up from study personel. Overall, there were slightly more adverse events in the treatment group compared to the placebo group; however, there were no serious adverse events noted in either the treatment or placebo group. A summary of the adverse events can be seen in the applicant's following table, which includes the number (and percentage) of subjects experiencing adverse events stratified by the treatment group (confirmed via JMP tabulations by the reviewing statistician).

Table 6.1.12.a. Summary of Adverse Events Observed in the Treated and Placebo Groups during the Entire Study Period

	Treatment group			
	Placebo (N = 240)		300 IR (N = 233)	
Description	**n**	**%**	**n**	**%**
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

n = number of patients with data, N = number of patients in each treatment group, % = percentage.
AE = adverse event, IR = index of reactivity, TEAE = treatment-emergent adverse event.
*Patient 1049/07 reported a SAE of malignant melanoma at the screening visit and was excluded from the study prior to randomization
Source: ***Section 14.3 Table 14.3.1/1*** results confirmed by reviewing statistician.

A summary of the types of serious adverse events observed during the study can be seen in the following table that was confirmed by the reviewing statistician via JMP. Within this table it can be seen that 4 patients had SAEs in the Placebo group and 2 patients had SAEs within the 300 IR group. Additionally other less serious adverse events are included within the applicant's below table with similar trends in adverse events occurring in both the active treated and placebo treatment groups.

Table 6.1.12.b. Summary of Serious Adverse Events

	Treatment group			
	Placebo (N = 240)		300 IR (N = 233)	
System Organ Class Preferred Term	n	%	n	%
Patients with at least one SAE	4	1.7	2	0.9
Gastrointestinal disorders	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
Infections and infestations	1	0.4	0	0.0
Gastroenteritis	1	0.4	0	0.0
Wound infection	1	0.4	0	0.0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0.0	1	0.4
Neuroendocrine carcinoma	0	0.0	1	0.4
Injury and poisoning	1	0.4	0	0.0
Ankle fracture, foot fracture, and joint dislocation	1	0.4	0	0.0

n = number of patients with data, N = number of patients in each treatment group, % = percentage.
IR = index of reactivity, PT = Preferred Term, SOC = System Organ Class, SAE = serious adverse event.
*Patient 1049/07 reported a SAE of malignant melanoma at the screening visit and was excluded from the study prior to randomization
Source: ***Section 14.3 Table 14.3.2/2*** results confirmed by reviewing statistician.

Additional details related to safety events can be seen in the Medical Officer's and Epidemiologist's reviews.

Safety Evaluation:

Reviewers comment: *Overall, the treatment group had slightly more adverse events than the placebo; however, as an active treatment designed to elicit a response via the product instead of the pollens during the pollen season, this finding is not surprising. Additional and more detailed comments can be found in the Medical Officer's and Epidemiologist's reviews.*

6.1.12.1 Methods

The safety data analysis consisted of examining observed Adverse Events provided by the applicant. Tabulations of adverse events were utilized to compare the effect of treatment versus placebo on the observation of adverse events. No pre-specified hypothesis tests were to be performed for either organ classes or specific adverse events. For further details and additional discussion, the statistician defers to the Medical Officer.

6.1.12.3 Deaths

No deaths were observed in this study in either treatment group.

6.1.12.4 Nonfatal Serious Adverse Events

No important findings were noted in the 6 observed non-fatal serious adverse events. The number of SAEs were fairly balanced between the two treatment groups (4 placebo and 2 active treatment) and all serious adverse events were self-limiting and were resolved upon discontinuation of study treatment. For further details and additional discussion, please refer to Medical Officer's review.

6.1.12.5 Adverse Events of Special Interest (AESI)

The statistician defers to the Medical Officer.

6.1.12.6 Clinical Test Results

Clinical Test results including IgG, IgE and other tests performed throughout the study had results that were expected and not considered outside of normal ranges. As per the Medical Officer "*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_4 will rise as IgE is falling. The rise in IgG_4 is known to accompany successful immunotherapy, though it cannot substitute as a biomarker for efficacy*". For further details and additional discussion, the statistician defers to the Medical Officer.

6.1.12.7 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 AEs.

Summary and conclusion: *Protocol VO61.08 met its objectives with respect to the primary efficacy endpoint, as well as several secondary endpoints. Additional subgroup analyses as well as sensitivity analyses provide supportive evidence that this product reduces the combined rescue medication and symptom scores, rescue medication use, and symptom scores when compared to placebo. The safety profile of ORALAIR® in this study appears to be acceptable, with only 4 serious adverse events that were all self-limiting and resolved. No deaths occurred.*

6.2 **Trial #2: V056.07-Chamber Study**

Protocol VO56.07 as proposed by the applicant is entitled "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." This was a Phase I Chamber Study not submitted under US-IND. However, it was suggested by the US-FDA that a chamber study be performed to provide supportive evidence that the Stallergenes Oralair® product reduces allergic symptoms in a controlled environment.

6.2.1 Objectives (Primary, Secondary, etc.)

Based on the protocol, the study had one primary objective and several secondary objectives related to both efficacy and safety endpoints.

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, and 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, and 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, and four months of treatment and at endpoint compared to placebo.
5) To document the safety of the treatment.

6.2.2 Design Overview

This was a Phase I study to examine adults age 18-50 years of age in a randomized, double blind, placebo controlled study in a single chamber site in Austria. Subjects were to be screened over the course of approximately 4 weeks, and those meeting eligibility requirements would be administered treatment for approximately 4 months. After the treatment period, subjects would be exposed to the 4 select grass allergens in an environmental chamber unit.

As per the applicant, "Environmental Exposure Chambers (EEC) are sealed rooms in which subjects may be exposed to pollen at specific levels (measured in grains/m^3) 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."

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 satisfied the screening criterion of an RTSS > 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 2nd EEC challenge at Week 1, a 3rd challenge at Month 1, a 4th challenge at Month 2, and a 5th challenge at Month 4 (Visit 7). Visit 8 was the last visit 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, which 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 pratens, Lolium perenne, and Phleum pratense was used. The duration of the initial EEC sessions was 2 hours, 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 minutes 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 seasons.

A more detailed description of the study can be found in the medical officer's review.

6.2.3 Population

The study population consisted of subjects from Austria 18-50 years of age who met specific inclusion/exclusion criteria. The most important criterion was the baseline RRTSS score of greater than or equal to 12, as well as seasonal grass pollen-related symptoms and measured reactions to ensure the individuals were sensitive to grass pollens.

6.2.4 Study Treatments or Agents Mandated by the Protocol

In this study, two treatments were to be examined and compared: Oralair® 300IR tablets and Placebo tablets that were indistinguishable from the 300IR Oralair® tablets. Both the active treatment and placebo were to be administered sublingually (under the tongue) every day at the same time during the approximate 4-month treatment period prior to the challenge exposure in the environmental chamber unit.

6.2.6 Sites and Centers

This study was conducted in one center in Vienna, Austria. This center was the location of clinic visits to obtain the study material, as well as the location of the environmental exposure challenge study.

6.2.7 Surveillance/Monitoring

The safety of the investigational product was evaluated by monitoring AEs 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.

The CRF forms for active surveillance were included in the BLA submissions and had been agreeable to the appropriate European regulatory authority under which this study was performed. Table 6.2.7.a. shows the schedule of study visits and monitoring. This table includes the time of study visits and the type of data and assessments to be collected at each time point stratified by the time frame/phase of the study (screening, treatment and follow-up).

Table 6.2.7.a. Schedule of Study Visits and Monitoring.

Assessments	Screening		Treatment period					Follow-up Discharge
	V1 Within 6 weeks prior to V3	V2 Any time between V1 and V3	V3 Week 0 Randomi-sation	V4 Week 1 (-3D;+3D)	V5 Month 1 (-3D; +7D)	V6 Month 2 (-7D; +7D)	V7 Month 4 (-7D; +7D)	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[1])	X	X	X	X	X	X	X	X
Urinary pregnancy test[2]–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[3]			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.

Source: applicant's BLA 125471/000; Clinical Study Report VO56.07, p.55

6.2.8 Endpoints and Criteria for Study Success

Primary efficacy assessment:

As per the applicant, the primary endpoint of interest was the average rhinoconjunctivitis total symptom score (ARTSS) collected during the [0-4] hours within the allergen chamber during the final challenge 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 were calculated as the mean of the RTSS at all time points (16 time points, from 15 minutes to four hours every 15 minutes) during the allergen exposure at endpoint. The ARTSS [0-4] hours can range between 0 and 18. The primary efficacy endpoint would be met if the decrease in ARTSS in the study drug group compared to the placebo group was $\geq$ 30% or a minimum difference in ARTSS of 1.2.

Secondary efficacy assessments:
1) The change from baseline in ARTSS [0-2] hours during the allergen challenge.
2) 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 Comment: *Although this study was not conducted under US-IND, the study was adequately designed and pre-specified to determine and test the effect of treatment versus placebo in an environmental chamber unit. It is up to the clinical reviewer to determine whether the criteria with respect to timing and minimum meaningful difference are acceptable.*

6.2.9 Statistical Considerations & Statistical Analysis Plan

As per the applicant, the pre-defined null hypothesis was described as no difference between treatment (300 IR) and Placebo groups in the RTSS after 4 months of pretreatment.

According to the applicant, this was the first environmental chamber study they had performed and as such no previous data in an allergen exposure chamber concerning grass pollen allergen extract SLIT was available. Consequently, the sample size was based on the following hypotheses conjectured by the applicant:

- 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 placebo effect with an improvement in ARTSS of at least 1.2.

Based on these assumptions, 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.

Based on an assumed 20% screening failure rate and a 15% drop-out rate, 100 subjects had to be screened in order to assure 40 randomized subjects in each group at the start of the study, and 34 at the end of study.

Reviewer Comment: *The power calculations that were provided by the applicant seem reasonable for an initial environmental chamber study.*

6.2.10 Study Population and Disposition

The following sections of this review provide insight into the study population and disposition of subjects examined and randomized in this study. Overall, it appears that very few subjects dropped out, and the demographics and disposition of subjects were similar between the two treatment arms.

6.2.10.1 Populations Enrolled/Analyzed

The safety population and the ITT population included all randomized subjects who received at least one dose of study medication. The PP population consisted of all completed subjects included in the ITT population, as well as subjects that discontinued or withdrew from the study.

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

As per the applicant predefined criteria, 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.

A summary of the study subject populations can be seen in the following table which includes the sample size and percentage of patients screened and randomized as well as the relevant analysis populations including safety, ITT and PP populations.

Table 6.2.10.1.a Number of Subjects in Each Population Treatment Group

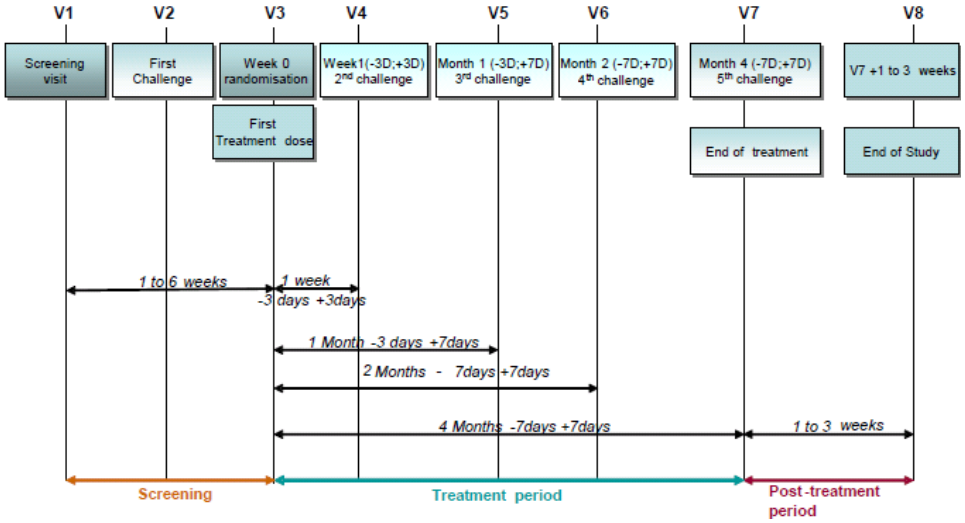
	SLIT		Placebo		Overall	
	n	%	n	%	n	%
Screened					97	
Randomised	45	100.0	44	100.0	89	100.0
Safety population	45	100.0	44	100.0	89	100.0
ITT population	45	100.0	44	100.0	89	100.0
PP population	42	93.3	41	93.2	83	93.3

Percentages are based on the number of randomised subjects
n = number of subjects, % = percentage of subjects

Source: Original BLA 125271; Clinical Study Report Study VO56-07; page 78, confirmed by reviewing statistician.

The study was to collect and examine data from enrolled and randomized subjects for several months. The following schematic provides insight into the study timing. Similar to the schedule visit and monitoring table this figure includes a diagram that illustrates the time of study visits and the type of data and assessments to be collected at each time point stratified by the time frame/phase of the study (screening, treatment and follow-up).

Figure 6.2.10.1.a. Design and Timing of Protocol VO56.07



Source: Original BLA 125471/000; Clinical Study Report VO56.07, p.48

The study was conducted after the 2007 grass pollen season and prior to the 2008 grass pollen season, *i.e.*, between the two seasons, which ensured minimal impact of grass pollens during the chamber study.

6.2.10.1.1 Demographics

The demographic characteristics of the treatment groups for the ITT population can be seen in the following table. This table includes the sample size and percentage as well as mean/standard deviation or median and quartiles of patients within the ITT population based on select demographics including: age, gender, ethnic origin and BMI.

Table 6.2.10.1.1.a. Summary of Demographic Characteristics-ITT Population

		SLIT (N=45)	Placebo (N=44)	Overall (N=89)
Age (years)	N	45	44	89
	Mean (SD)	27.46 (6.577)	27.12 (5.807)	27.29 (6.175)
	Median	25.30	25.74	25.64
	Q1-Q3	24.06 – 28.22	23.61 – 29.30	23.72 – 29.12
	Min-Max	19.7 – 49.8	18.6 – 46.6	18.6 – 49.8
Gender	Female	24 (53.3%)	28 (63.6%)	52 (58.4%)
	Male	21 (46.7%)	16 (36.4%)	37 (41.6%)
Ethnic origin	Caucasian	45 (100.0%)	44 (100%)	89 (100.0%)
	Black	0	0	0
	Asian/Pacific Islander	0	0	0
	Other	0	0	0
BMI* (kg/m^2)	N	45	44	89
	Mean (SD)	22.31 (2.824)	22.50 (3.259)	22.40 (3.031)
	Median	21.83	22.12	21.90
	Q1-Q3	20.20 – 23.77	19.93 – 24.37	20.11 – 24.22
	Min-Max	17.6 – 28.2	17.3 – 32.0	17.3 – 32.0

* Body Mass Index = weight (kg) / height^2 (m)

Source: Original BLA 125271; Clinical Study Report Study VO56-07; page 83 confirmed by reviewing statistician.

Reviewer Comment: *Considering the results presented in the above table, confirmed by the reviewing statistician, 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.*

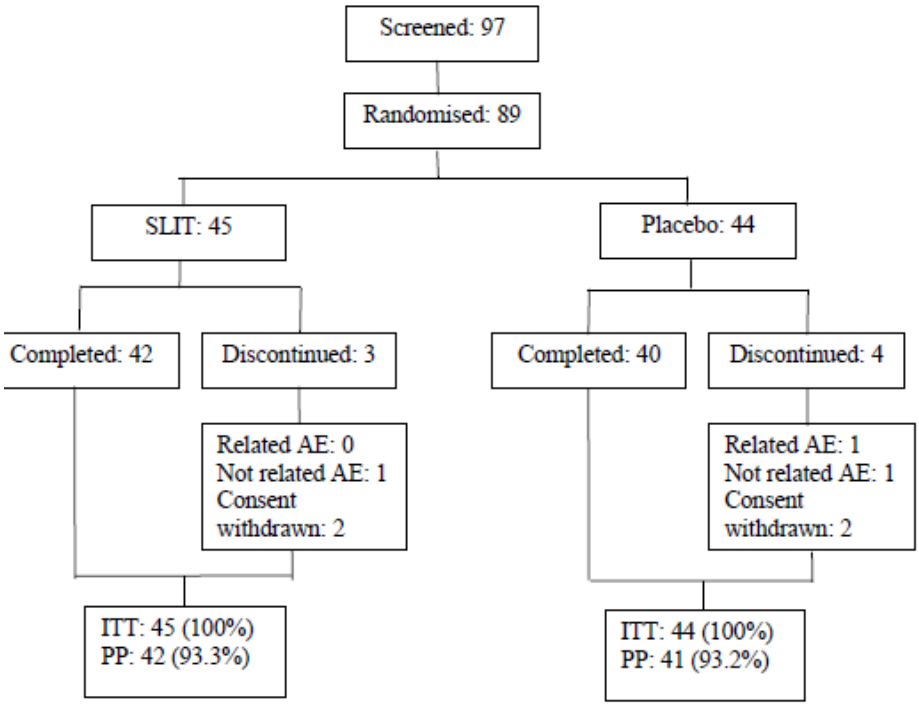
6.2.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

This study was performed at a single site, and for the primary efficacy variable explored less than 4 hours of data. Thus, very few medical/behavioral characteristics would have been observed, other than symptoms related to exposure to the pollen that was being administered in the environmental chamber unit.

6.2.10.1.3 Subject Disposition

The following figure illustrates the randomization, allocation, and withdrawal of patients for this study. This graphic notes which treatment arm subjects were randomized to and subsequently lists the reason for dropout including the number of subjects and percentage of subjects that withdrew prior to study completion. It is of interest to note the adverse event rate is slightly higher in the active treatment group; however, other reasons for dropout were fairly similar between the placebo and treatment groups.

Table 6.2.10.a. Subject Disposition



Source: Original BLA 125271; Clinical Study Report Study VO56-07; page 78

Based on the above table, approximately 45 and 40 individuals per treatment arm were included in the ITT analysis group and PP analysis group, respectively, and no notable imbalances occurred.

6.2.11 Efficacy Analyses

In this study, the subjects were to be administered 4 months of active treatment or placebo. Subjects at pre-defined time points were to be exposed to pollen for 4 hours in a chamber unit in which allergic symptoms were to be collected every 15 minutes at environmental challenge visits, including baseline, week 1 post-dose, month 1 post-dose, month 2 post-dose, and month 4 post-dose. The primary efficacy analysis was to examine various allergenic symptoms and determine if there was a difference between the study drug and placebo groups after 4 months of treatment during the final 4-hour environmental chamber exposure. However, other efficacy analyses were also to be performed.

6.2.11.1 Analyses of Primary Endpoint(s)

The primary efficacy variable was the difference in the RTSS between the study drug and placebo groups after 4 months of treatment during the 4 hour environmental chamber exposure. As per the applicant, the first assessment that was to be performed was to determine if the two study groups were equally affected at baseline by the EEC exposure. Once equanimity was assured, the analysis could proceed. The primary efficacy analysis was to examine chamber average rhinoconjuctivitis symptom score (ARTSS) utilizing

ANCOVA based on the treatment assignment and baseline ARTSS value at month 4 post-dose.

Table 6.2.11.1.a. Comparison of Treatment Groups for the ARTSS [from 0-4 hours]-ITT Population at the 4-month Challenge[1]

Treatment	N	LS Mean (SE)	LS Mean difference vs Placebo Point Est	LS Mean difference vs Placebo 95% CI
SLIT	42	4.88 (0.36)	-1.96	[-2.99, -0.94]
Placebo	40	6.84 (0.37)		

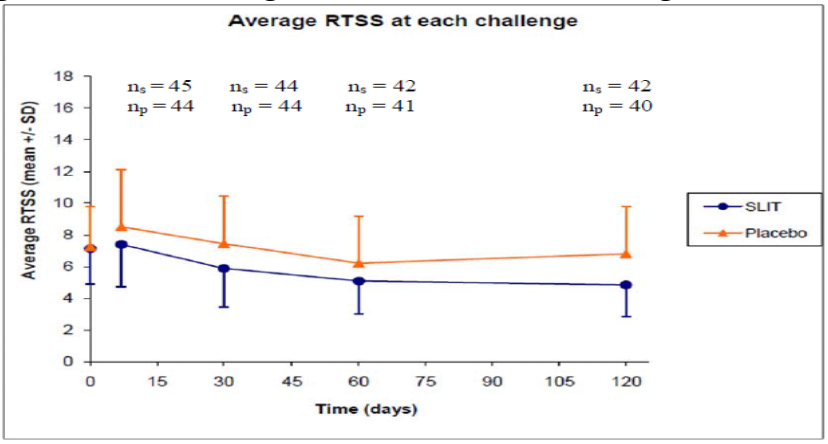
[1] ANCOVA: treatment effect fixed and including baseline ARTSS as covariate
Source: Statistical reviewer's table, confirming results in sBLA 125471/000, Clinical Study Report VO56.07 page 89. Note data file location is:
----------(b)(4)----------

From the above table it can be seen that there is a reduction of symptoms in the environmental chamber study in the SLIT treated subjects compared to the placebo control group.

6.2.11.2 Analyses of Secondary Endpoints

The secondary endpoints included the RTSS during the additional chamber exposures (baseline, week 1, month 1, month 2, and month 4). A summary of these data is best examined utilizing the applicant figure (below), which displays the SLIT and placebo RTSS responses. This figure illustrates the reduction of symptom scores when comparing the active treatment to placebo during each of the chamber studies at day 15, 30, 60 and 120. Within the figure the means and confidence bounds based on the RTSS score are also provided illustrating the improvement of symptom scores within subjects randomized to active treatment when compared to those administered placebo.

Figure 6.2.11.2. Average RTSS at Each ECC Challenge



Source: Original BLA 125471/000; Clinical Study Report VO56.07, p.97

These results can be further examined in a tabulation of results, shown in Table 6.2.11.2.a below. The table below illustrates numerically based on the LSMeans as well as

LSMeans difference and 95% CI based on the RTSS when comparing the active treatment to placebo during each of the chamber studies days 7, 15, 30, 45 and 120 post treatment. Within the table the means and confidence bounds based on the RTSS score are also provided illustrating the improvement of symptom scores within subjects randomized to active treatment when compared to those administered placebo

Table 6.2.11.2.a. Comparison of Treatment Groups for the ARTSS [from 0-4 hours]-ITT Population for All Challenge Exposures[1]

Timing	Treat-ment	N	LS Mean (SE)	LS Mean difference vs Placebo Pt Est	LS Mean difference vs Placebo 95% CI
Week 1	SLIT	45	7.43 (0.39)	-1.04	[-2.14 ; 0.07]
	Placebo	44	8.47 (0.39)		
Month 1	SLIT	44	5.94 (0.35)	-1.46	[-2.45 ; -0.47]
	Placebo	44	7.40 (0.35)		
Month 2	SLIT	42	5.09 (0.33)	-1.12	[-2.05 ; - 0.18]
	Placebo	41	6.21 (0.33)		
Month 4	SLIT	42	4.88 (0.36)	-1.96	[-2.99, -0.94]
	Placebo	40	6.84 (0.37)		

[1] ANCOVA: treatment effect fixed and including baseline ARTSS as covariate
Applicant ANCOVA factors: treatment and time, interaction: treatment*time and covariate: baseline values
Source: Statistical reviewer's results, similar to applicant's Table 11.4.1 in sBLA 125471/000; Clinical Study Report VO56.07 page 99. Note data is located at:
----------(b)(4)----------

Reviewer Comment: *Based on the results provided by the applicant and confirmed by the reviewing statistician, it appears that this product does reduce ARTSS when compared to the placebo control in the various environmental challenges that occurred within this study.*

6.2.11.3 Subpopulation Analyses

This was a relatively small phase I study (approximately 45 subjects per treatment arm), so no subpopulations were to be analyzed. Furthermore, in this study only Caucasian individuals were included, and the study examined individuals 18-50 years of age; thus, stratification by race and age was not done. No differences in subject ARTSS responses based on gender were noted.

6.2.11.4 Dropouts and/or Discontinuations

Several subjects dropped out at various time points during the study, and these discontinuations are further discussed in the medical officer's review. However, there were no missing data during the allergen challenges, except for a nasal secretion weight at one time point and for one subject. Thus, missing values were not an issue in this study.

6.2.11.5 Exploratory and Post Hoc Analyses

The applicant provided extensive results of post-hoc analyses, some of which were also examined by the reviewing statistician. However, for such a small Phase I clinical trial, exploratory and post hoc analyses are of limited value and thus not presented in this review.

6.2.12 Safety Analyses

6.2.12.1 Methods

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

6.2.12.3 Deaths

There were no deaths reported during this study.

6.2.12.4 Nonfatal Serious Adverse Events

There were no non-fatal serious adverse events reported during this study.

6.2.12.5 Adverse Events of Special Interest (AESI)

There were slightly more drug-related AEs in the treatment group, and more AEs that led to study withdrawal in the treatment group, compared to the placebo group. Most of the AEs 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) and did not require discontinuation of therapy.

A Summary of the AEs can be seen in the following table, which was confirmed by the reviewing statistician via tabulations within JMP.

Table 6.2.12.5.a. Observations of Adverse Events in the Safety Analysis Population

	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

Percentages are based on the number of subjects in the Safety population
n = number of subjects, % = percentage of subjects
Source: BLA 125471/000; Clinical Study Report VO56.07, p.123, confirmed by reviewing statistician

These AEs can be further examined in the following table, which summarizes the Adverse Events that occurred in at least 5% of subjects. These results were confirmed by the reviewing statistician.

Table 6.2.12.5.b. Adverse Events Occurring in at Least 5% of Subjects in the Safety Analysis Population

System Organ Class	SLIT (N=45)			Placebo (N=44)		
Preferred term	nAE	n	%	nAE	n	%
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
*: TEAE are defined as events that started on or after the first dose of the investigational product
Source: BLA 125471/000; Clinical Study Report VO56.07, p.124, confirmed by reviewing statistician.

6.2.12.6 Clinical Test Results

Clinical Test results varied between and within the individuals within this study however, endpoints including IgG, IgE and other tests performed had results that were expected and not considered outside of normal ranges. The statistical reviewer defers to the medical officer for additional comments on clinical test results.

6.2.12.7 Dropouts and/or Discontinuations

There were three dropouts due to AEs. These dropouts are discussed in more detail within the medical officer's review.

6.2.13.1 Study Summary:

In Protocol VO56.07, subjects who were treated with ORALAIR® for four months had an ARTSS that was 28.7% lower than in the placebo group (95% CI: 13.7%; 58.3%). This decrease does not meet the applicant pre-specified decrease of 30%; however, the confidence interval suggests that the product does reduce symptoms during the chamber challenge. The point estimate of the difference in ARTS Score was observed to be 1.96, which was above the proposed minimum difference of 1.2. AEs were mild or moderate, and there were no SAEs.

Reviewer Comment: *This Phase I environmental chamber study was not performed under US-IND; however, based on the results presented by the applicant and additional analysis performed by the reviewing statistician, it appears that this product does reduce rhinoconjunctivitis symptoms. However, because this study was performed in one site within Austria, generalizations to other sites and countries should be made with caution.*

6.3 **Trial #3: VO52.06**

Study VO52.06 was included to examine the effect of Oralair® SLIT on pediatric patients 5-17 years of age. This study was not performed under US-IND but did utilize a pre-specified Protocol defined as Study V052.06, described as, *"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."*

6.3.1 Objectives (Primary, Secondary, etc.)

The following provides details of the primary and secondary objectives as proposed by the applicant.

Primary Objective:
To assess the efficacy of SLIT for grass pollen allergens on the Rhinoconjunctivitis Total Symptom Score (RTSS) of the six rhinoconjunctivitis symptoms (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.

6.3.2 Design Overview

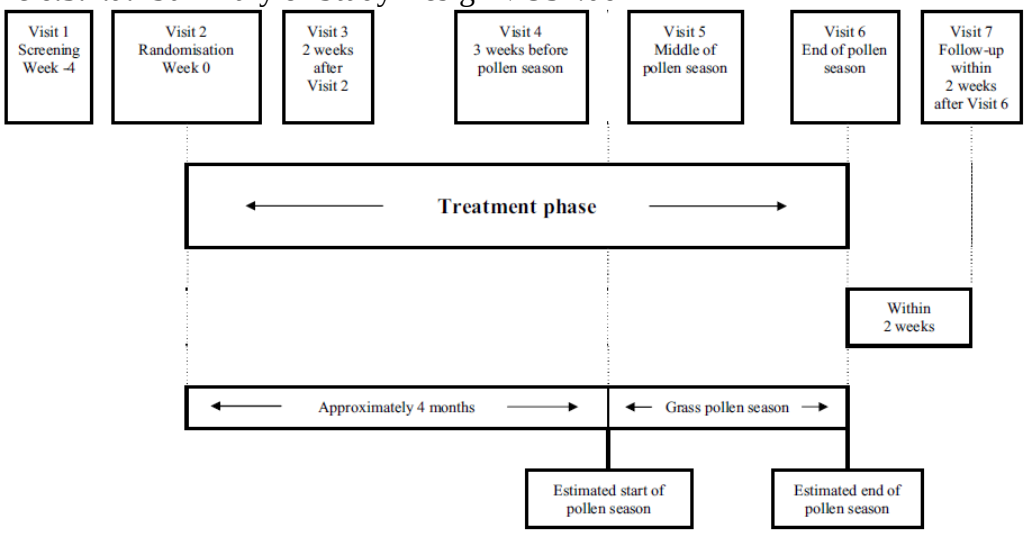
Protocol VO52.06 was a randomized Phase 3, double-blind, placebo-controlled trial of safety and efficacy of ORALAIR, 300 IR, in children and adolescents 5-17 years of age

in northern Europe. There were 29 centers located in Denmark, France, Germany, Poland, and Spain.

Once randomized, subjects were to be treated for approximately 8 months with an additional month of follow-up. Data were to be collected on both safety and efficacy endpoints.

A summary of the study timing and design can be seen in the following figure. This figure illustrates the timing of the study in detailed graphical format starting with Visit 1: screening through Visit 7: Follow-up within 2 weeks after Visit 6. This figure also provides both an illustration of the timing of the treatment phase as well as the anticipated pollen season.

Figure 6.3.2.a. Summary of Study Design VO52.06



Source: Original BLA 125471/000; Clinical Study Report VO52.06, p. 26

6.3.3 Population

Study VO52.06 included children 5-17 years of age with acceptable allergenic response to grasses based on ARC, positive skin prick test, as well as pre-study RTSS score. Additional details on the inclusion/exclusion criteria can be found in the medical officer's review.

6.3.4 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. On Day 2, the placebo group received two tablets of placebo as expected to maintain the blind within the 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.

6.3.6 Sites and Centers

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

6.3.7 Surveillance/Monitoring

The safety of the investigational product was evaluated by monitoring AEs 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.

6.3.8 Endpoints and Criteria for Study Success

The Primary Endpoint of interest was the detection of efficacy as defined by a mean decrease of 20% of the ARTSS. This analysis was to be similar to the previously

described phase III environmental exposure field study (study 61.08US) and was to incorporate various fixed and random covariates in the statistical model.

The Secondary Endpoints of Interest were:

- Rescue medication usage (Average RMS)
- Average CS
- Average RSS

Similar statistical models for the primary endpoint were to be utilized to examine the secondary endpoints.

6.3.9 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 study enrolled 350 individuals based on the following power and sample size calculations. 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 would 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.

6.3.10 Study Population and Disposition

The following section describes the study population and disposition for subjects enrolled and randomized in this study.

6.3.10.1 Populations Enrolled/Analyzed

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.

6.3.10.1.1 Demographics

The demographics of the treatment groups were provided by the applicant and confirmed by the reviewing statistician via JMP. The results of the tabulations can be seen from the below table. This table includes the sample size (n) and percentage of individuals for several analysis sets (Safety, ITT and PP) based on age, gender, height, weight and BMI stratified by treatment group. Overall the demographics appear to be similar between the analysis sets and treatment groups; however, it is of note that there are more males in this study than females.

Table 6.3.10.1.1.a. Summary of Demographic Characteristics

Variable		Population					
		Safety		ITT		PP	
Treatment Group		n	%	n	%	n	%
Gender		**139**	**100.0%**	**131**	**100.0%**	**112**	**100.0%**
300 IR	Female	46	33.1%	45	34.4%	38	33.9%
	Male	93	66.9%	86	65.6%	74	66.1%
		139	**100.0%**	**135**	**100.0%**	**115**	**100.0%**
Placebo	Female	50	36.0%	50	37.0%	40	34.8%
	Male	89	64.0%	85	63.0%	75	65.2%
		278	**100.0%**	**266**	**100.0%**	**227**	**100.0%**
All	Female	96	34.5%	95	35.7%	78	34.4%
	Male	182	65.5%	171	64.3%	149	65.6%
Age group (years)		**139**	**100.0%**	**131**	**100.0%**	**112**	**100.0%**
300 IR	5 to 11	87	62.6%	82	62.6%	69	61.6%
	12 to 17	52	37.4%	49	37.4%	43	38.4%
		139	**100.0%**	**135**	**100.0%**	**115**	**100.0%**
Placebo	5 to 11	74	53.2%	71	52.6%	60	52.2%
	12 to 17	65	46.8%	64	47.4%	55	47.8%
		278	**100.0%**	**266**	**100.0%**	**227**	**100.0%**
All	5 to 11	161	57.9%	153	57.5%	129	56.8%
	12 to 17	117	42.1%	113	42.5%	98	43.2%

	Safety		ITT		PP	
	Mean (SD)	Range[a]	Mean (SD)	Range[a]	Mean (SD)	Range[a]
Age (years)						
300 IR	10.6 (3.30)	4 – 17	10.5 (3.34)	4 – 17	10.8 (3.22)	4 – 17
Placebo	11.2 (3.04)	5 – 17	11.2 (3.07)	5 – 17	11.3 (3.11)	5 – 17
All	**10.9 (3.18)**	**4 – 17**	**10.9 (3.22)**	**4 – 17**	**11.0 (3.17)**	**4 – 17**
Weight (kg)						
300 IR	41.1 (15.50)	17 – 85	40.9 (15.58)	17 – 85	42.5 (15.40)	17 – 85
Placebo	44.3 (16.47)	19 – 116	44.4 (16.63)	19 – 116	44.6 (17.16)	19 – 116
All	**42.7 (16.05)**	**17 – 116**	**42.7 (16.19)**	**17 – 116**	**43.6 (16.31)**	**17 – 116**
Height (cm)						
300 IR	146.6 (18.93)	109 – 190	146.2 (19.06)	109 – 190	147.9 (18.19)	109 – 190
Placebo	150.1 (17.02)	98 – 185	150.1 (17.14)	98 – 185	150.3 (17.22)	98 – 185
All	**148.3 (18.05)**	**98 – 190**	**148.2 (18.19)**	**98 – 190**	**149.1 (17.70)**	**98 – 190**
BMI (kg/m^2)						
300 IR	18.4 (3.23)	11 – 27	18.4 (3.27)	11 – 27	18.7 (3.25)	14 – 27
Placebo	19.0 (3.86)	13 – 37	19.0 (3.91)	13 – 37	19.1 (4.05)	13 – 37
All	**18.7 (3.57)**	**11 – 37**	**18.7 (3.62)**	**11 – 37**	**18.9 (3.67)**	**13 – 37**

n = Number of patients; % = Percentage of patients; BMI: Body Mass Index; IR: Index of reactivity;
ITT: Intention to Treat; PP: Per Protocol; SD: Standard deviation.
[a] Range = Minimum value to Maximum value.

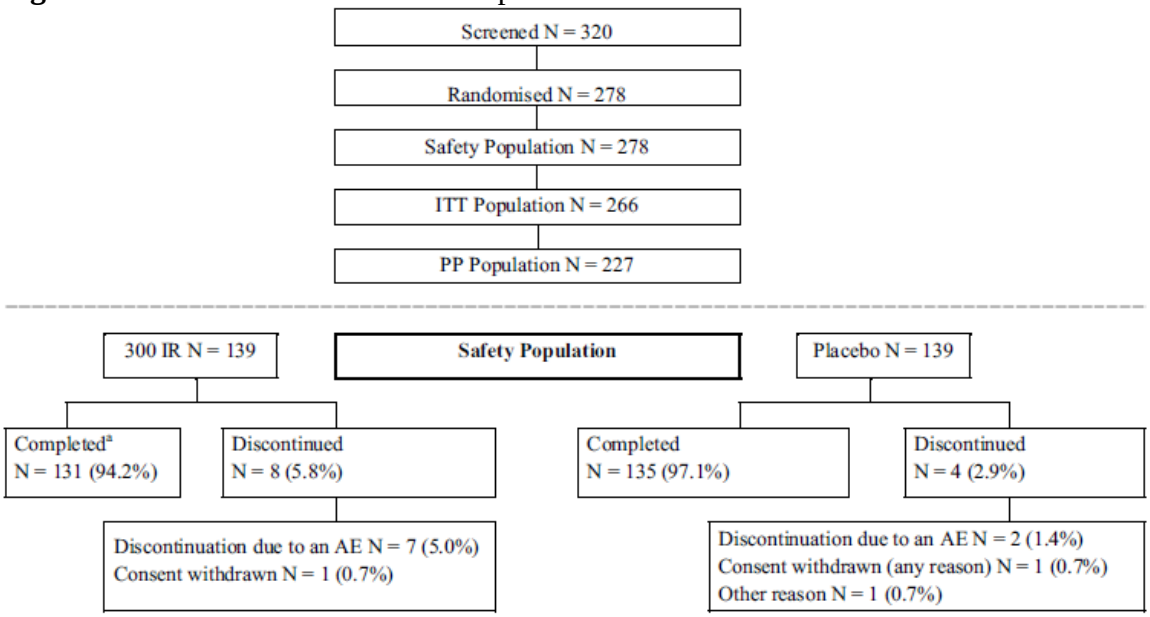
Source: Original BLA 125471/000; Clinical Study Report VO52.06, p. 58, confirmed by reviewing statistician

6.3.11 Efficacy Analyses

A more detailed schematic of subjects enrolled and randomized including the various analysis sets in this study can be seen in the following figure. This schematic identifies the patients in the Safety, ITT and PP analysis sets. Within this schematic it can be seen

that the patients randomized, treated and completed the study are fairly comparable between treatment groups. The discontinuation of individuals in the treated group is slightly higher when compared to the treated group with 8 (5.8%) and 4 (2.8%) subjects discontinuing in the treated versus placebo groups respectively.

Figure 6.3.10.1.a. Overall Patient Disposition



N = Number of patients; % = Percentage of patients; AE: Adverse event; IR: Index of reactivity; ITT: Intention to Treat; PP: Per Protocol.
[a] 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: Original BLA 125471/000; Clinical Study Report VO52.06, p. 54

6.3.11.1 Analyses of Primary Endpoint(s)

Study VO52.06 Efficacy Results:

Protocol VO52.06 was designed to evaluate its pre-defined 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 can be seen in the below table confirming the applicant results in the BLA application, the study met its primary endpoint utilizing an ANCOVA Model with treatment, pooled centers, baseline/retrospective symptom score (RRTSS), Age, Gender, Asthma, and Grass Sensitization Status.

Table 6.3.11.1.a. Average RTSS over entire Pollen Season: ANCOVA- ITT Population

Treatment	N	LS Mean	LS Mean difference vs Placebo Pt Est	LS Mean difference vs Placebo 95% CI	Percent (%) % Difference	Percent (%) 95% CI
300 IR	131	3.31	-1.13	[-1.80, -0.46]	-25.6%	[-40.4%, -10.3%]
Placebo	135	4.45				

Source: Statistical reviewer confirmation of results adapted from BLA 125471/000; Clinical Study Report VO52.06, p.131

The results presented in the above table illustrate that the ARTSS in the ITT population was decreased by a % Reduction in Symptoms of 25.6%, with 95% CI [-40.4, -10.3%] over the entire GPS. A comparable decrease over the "worst pollen period" (defined as the most intensive pollen period over approximately 10 to 14 days per study center) was also observed.

Reviewer comment: *The ANCOVA model incorporated Treatment, Pooled Sites, Age, Baseline RRTSS (retrospective), Age, Gender, Asthma Status, and Sensitization as covariates. The pooling of sites was pre-specified and may be reasonable; however, this then may collapse the inherit variability of the pollen counts as well as specific site effects. Additionally, the use of retrospective measurements based on the subject's recall of symptoms occurring prior to baseline rather than collecting the symptoms explicitly during a predefined baseline/pre-treatment time period may introduce bias. However, since the retrospective measures were collected at baseline and did not affect treatment allocation, the effect of this potential source of bias should be limited by the randomization procedures.*

6.3.11.2 Analyses of Secondary Endpoints

The applicant proposed to examine the following secondary endpoints in this study:

- Rescue medication usage (Average RMS)
- Average CS.

A summary of the results of the secondary endpoints can be seen in the following table. This table provides the endpoint, treatment, sample size as well as the calculated LSMean as well as the point estimate and 95% CI of the mean difference between treatment and placebo based on the pre-specified ANCOVA model with treatment, pooled centers, baseline symptom score, Age, gender, asthma and grass sensitization status.

Table 6.3.11.2 Presentation of Results of Secondary Endpoints-Entire Pollen Season-ITT Analysis Population

Endpoint	Treatment	N	LS Mean	LS Mean difference Treatment vs Placebo Point Est	LS Mean difference Treatment vs Placebo 95% CI
				-0.20	[-0.34, -0.06]
	Placebo	135	0.73		
Average CS	300 IR	131	0.54	-0.19	[-0.30. -0.09]
	Placebo	135	0.73		

Source: Statistical Reviewer results based on confirmatory analysis utilizing the ANCOVA Model with treatment, pooled centers, baseline/retrospective symptom score (RRTSS), Age, Gender, Asthma, and Grass Sensitization Status

These results are similar and consistent with the primary efficacy variable and appear to support the contention that this product reduces symptoms and use of rescue medication when compared to placebo.

6.3.11.3 Subpopulation Analyses

No subpopulation analyses based on age or race were performed due to the small sample size of this study. This study included only youth 5-17 years of age and there were less than 5 individuals in any race other than white/caucasian. Similar results and conclusions regarding the efficacy of this product were seen when comparing males and females. Other select subpopulation analysis were performed including baseline IgG, geographic region and asthma status yielded similar conclusions regarding the efficacy of Oralair®

6.3.11.4 Dropouts and/or Discontinuations

As per the applicant, 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 (a multiple imputation mechanism) within 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.

Reviewer Comment: *This study was not submitted or performed under US-IND, as it was an international/European study in children 5-17 years of age. It appears these missing data mechanisms were pre-specified and appear to be reasonable, particularly when a variety of sensitivity analyses were performed and supported the similar results and conclusions.*

6.3.11.5 Exploratory and Post Hoc Analyses

A variety of exploratory and post-hoc analyses were provided by the applicant. The main post-hoc exploratory analysis of interest to the clinical reviewer included: Immunological markers, skin prick test, and asthma evaluation. These results can be seen in the medical officer's review, but should be interpreted with caution since the study was not designed to examine these endpoints.

6.3.12 Safety Analyses

The safety of this product was analyzed using the safety analysis dataset and included all subjects randomized and administered at least one dose of study treatment.

6.3.12.1 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 assessment of routine clinical laboratory safety tests (performed at screening and end of treatment). Additional details on the safety data can be seen in the medical officer's and epidemiologist's reviews.

6.3.12.3 Deaths

No deaths were observed in this study.

6.3.12.4 Nonfatal Serious Adverse Events

One subject in the treatment group and one subject in the placebo group were found to have serious non-fatal adverse events. Further details can be seen in the medical officer's review. However, these AEs were assessed by both the applicant applicantand the Agency's medical officer to be not related to the study drug administration.

6.3.12.5 Adverse Events and Adverse Events of Special Interest (AESI)

In this study there were a variety of adverse events reported. As noted previously, there were no SAEs or deaths.

The incidence of respiratory disorders in each study group was similar. However, there were more drug-related AEs in the treatment group, particularly related to the gastro-intestinal issues. A summary of the Adverse Events observed during this study can be seen in the following table. This table provides the number and percentage of individuals experiencing adverse events as well as the size of the safety analysis set for the active treatment and Placebo treated groups. The listing of adverse events stratified by treatment groups is further expanded by the organ class affected.

Table 6.3.12.5.a. Incidence of Treatment-Emergent Reported Adverse Events Reported by Greater Than 5% of Patients, by Organ Class

	Treatment group					
	300 IR			Placebo		
SOC	N = 139			N = 139		
PT	n	m	%	n	m	%
Number of patients with TEAEs[a,b]	**118**	**500**	**84.9%**	**114**	**402**	**82.0%**
Respiratory, thoracic and mediastinal disorders	**74**	**176**	**53.2%**	**70**	**163**	**50.4%**
Cough	35	65	25.2%	37	55	26.6%
Sneezing	11	11	7.9%	11	12	7.9%
Nasal congestion	12	12	8.6%	9	9	6.5%
Wheezing	8	8	5.8%	13	18	9.4%
Throat irritation	13	13	9.4%	7	10	5.0%
Rhinorrhoea	8	9	5.8%	10	12	7.2%
Asthma	10	20	7.2%	6	6	4.3%
Nasal discomfort	7	8	5.0%	9	9	6.5%
Epistaxis	3	3	2.2%	9	10	6.5%
Infections and infestations	**55**	**82**	**39.6%**	**58**	**92**	**41.7%**
Nasopharyngitis	19	22	13.7%	18	22	12.9%
Pharyngitis	6	8	4.3%	16	17	11.5%
Tonsillitis	9	10	6.5%	5	5	3.6%
Gastrointestinal disorders	**70**	**134**	**50.4%**	**23**	**25**	**16.5%**
Oral pruritus	46	61	33.1%	6	6	4.3%
Oedema mouth	18	19	12.9%	0	0	0.0%
Lip swelling	7	7	5.0%	1	1	0.7%
Eye disorders	**14**	**20**	**10.1%**	**25**	**35**	**18.0%**
Eye pruritus	10	11	7.2%	12	13	8.6%
Conjunctivitis	4	4	2.9%	7	8	5.0%
Lacrimation increased	2	2	1.4%	8	8	5.8%
Nervous system disorders	**12**	**20**	**8.6%**	**24**	**32**	**17.3%**
Headache	11	17	7.9%	24	32	17.3%

m = Number of mentions; N = Number of patients; n = Number of patients with TEAEs; % = Percentage of patients;
MedDRA: Medical Dictionary for Regulatory Activities; IR: Index of reactivity; PT: Preferred Term;
SOC: System Organ Class; TEAE: Treatment-emergent adverse event.
[a] Treatment-emergent adverse events are defined as events that started on or after the first dose of the investigational product.
[b] Adverse events were coded using MedDRA Version 9.1.

Source: BLA 125471/000; Clinical Study Report VO52.06, p.80

Additional details and descriptions of patients and adverse events can be seen in the medical officer's review.

6.3.12.6 Clinical Test Results

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

6.3.12.7 Dropouts and/or Discontinuations

Two subjects dropped out/withdrew from the placebo arm and seven subjects dropped out of the 300 IR treatment arm. Further details about these patients can be seen in the medical officer's and epidemiologist's reviews.

There were several additional efficacy studies provided by the applicant; however, these were smaller Phase I/II studies, they were not performed in the US or under US-IND, they were not considered pivotal, or they were safety studies. These studies and relevant results will be included in the integrated overview of efficacy.

7. INTEGRATED OVERVIEW OF EFFICACY

The following section summarizes the totality of evidence combining the results of all studies submitted by the applicant to this BLA. Based on the results presented by the applicant and confirmed by the reviewing statistician, it appears this product reduces daily symptom scores, reduces the use of daily rescue medication and reduces the combined symptom score that incorporates both the daily allergic symptoms as well as the use of rescue medication.

7.1 Indication #1

Based on the applicant provided Label and Package Insert, the following is the proposed indication for this product:

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

Overall, 2,512 patients participated in the clinical development program of ORALAIR®, which consisted of eight clinical trials, of which six included efficacy endpoints. The effectiveness of ORALAIR® was evaluated in six randomized, double-blind, placebo-controlled clinical trials: VO34.04 (European study), VO61.08USA (US study), VO56.07A (allergen exposition chamber study), VO52.06 (Pediatric study), VO53.06 (Long Term study), and VO60.08 (alternate regimen study) either in adults (VO34.04, VO61.08USA, VO56.07A, and VO53.06), adolescents and children (VO52.06), or both (VO60.08).

The Summary of Clinical Efficacy presents a comprehensive analysis of the six efficacy studies supporting the approval of ORALAIR® for the treatment of grass pollen-induced allergic rhinoconjunctivitis.

A tabular listing of the six efficacy studies submitted to the Agency within this BLA is provided below. This table includes a summary of the study location, population examined, treatment regimen, and dosage administered.

Table 7.1.1.a. Efficacy Studies provided within the BLA for Stallergenes Oralair®

Study	Location of the clinical center(s)	Population	Initiation phase[1]	Treatment regimen	Maintenance phase dosage
VO34.04	Europe	Adults	Yes	A pre- and co-seasonal administration regimen (starting 4 months before the grass pollen season) conducted over a single pollen season	500 IR 300 IR 100 IR
VO61.08USA	USA	Adults	No	A pre- and co-seasonal administration regimen (starting 4 months before the grass pollen season) conducted over a single pollen season	300 IR
VO56.07A	Europe	Adults	No	Approximately 4-months, outside the grass pollen season (allergen exposition chamber)	300 IR
VO52.06	Europe	Children and adolescents	Yes	A pre- and co-seasonal administration regimen (starting 4 months before the grass pollen season) conducted over a single pollen season	300 IR
VO53.06	Europe, Canada, Russia	Adults	No	A pre- and co-seasonal administration regimen for three treatment years followed by two immunotherapy-free pollen seasons	300 IR
VO60.08	Europe	Adults and adolescents	No	A pre- and co-seasonal administration regimen (starting 2 months before the grass pollen season) conducted over a single pollen season	300 IR

Source: Original BLA application 125471/000 ISE page 10

From the above table and previously examined studies in this review, it can be seen that the majority of the studies examined the efficacy of treatment in natural exposure field studies after 4 months of treatment over one grass pollen season.

The primary proof for efficacy, as per CBER Standards, is the (CS) combined score, which incorporates both the rescue medication score as well as the rhinoconjunctivitis symptom score during the pollen season. However, since many of these studies were performed internationally and not under US-IND, the pre-specified primary efficacy endpoints varied between studies.

Integration of results was to incorporate both the primary endpoints as well as secondary endpoints of the various studies in order to utilize and compare the CS as the primary efficacy endpoint. Furthermore, the clinically meaningful difference was to be set utilizing the US standard, based on the May 2011 Advisory Committee agreed upon standard of -10% as the clinically meaningful upper bound for the % difference between treatment and placebo responses in the CS endpoint.

The following table provides a summary of endpoints based on protocols submitted by the applicant and consists of all studies considered within the integrated study of efficacy.

This table includes a listing of primary and key secondary endpoints, the study, as well as they type of analysis performed stratified by study.

Table 7.1.1.b. Summary of Endpoints based on Protocols submitted by Stallergenes and considered for the Integrated Study of Efficacy

Endpoint	VO34.04	VO61.08USA	VO52.06	VO53.06*
Daily CS	*Post hoc analysis*	**Primary**	*Post hoc analysis*	*Post hoc analysis*
Daily RTSS	*Post hoc analysis*	Secondary	*Post hoc analysis*	*Post hoc analysis*
Daily RMS	*Post hoc analysis*	Secondary	*Post hoc analysis*	*Post hoc analysis*
Daily ASS	-	Secondary	-	-
ACS	*Post hoc analysis*	Secondary	Secondary	Secondary
ARTSS	**Primary**	Secondary	**Primary**	Secondary
ARMS	*Post hoc analysis*	Secondary	Secondary	Secondary
AASS	*Post hoc analysis*	Secondary	*Post hoc analysis*	**Primary**
RQLQ	Secondary	Secondary	-	Secondary
Global evaluation of treatment efficacy by patient	Secondary	Secondary	Secondary	Secondary

AASS = Average Adjusted Symptom Score; ACS = Average Combined Score; ARMS = Average Rescue Medication Score; ARTSS = Average Rhinoconjunctivitis Total Symptom Score; ASS = Adjusted Symptom Score; CS = Combined Score; RMS = Rescue Medication Score; RTSS = Rhinoconjunctivitis Total Symptom Score; RQLQ = Rhinoconjunctivitis Quality of Life Questionnaire
*study VO53.06: the primary efficacy endpoint was the AASS in the Year 3 pollen season.

Source: Original BLA application 125471/000 ISE page 45

In all studies, the primary efficacy endpoint [i.e., the symptom score or symptom/rescue medication score, (dependent variable)] was analyzed using a linear model, specifically an ANCOVA with treatment as main effect, pooled study center as stratification factor for the multicenter studies, and several covariates (including: age, gender, baseline symptom/rescue medication scores) which could potentially impact the clinical score.

7.1.2 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. It is also of note that the racial profile of subjects was predominantly white/Caucasian in all studies performed by the applicant. In various studies, the distribution of gender did slightly differ as can be seen in the below table (in which males tended to be more common with 45% to 66% of participants and females varied from 34% to 55% of participants); however, in the randomized treatment groups, no imbalance was noted. Specific details related to demographic and baseline characteristics can be seen in the following table will examines the number and percentage of individuals in the Full Analysis set stratified by treatment group including the following variables: age, gender, race/ethnicity, BMI, asthma status, sensitivity to grass pollens, and baseline retrospective symptom scores.

Table 7.1.2.a. Summary of Demographic and Baseline Characteristics

	VO34.04					VO61.08USA			VO52.06			VO53.06 Year 1			
	500 IR (4M) N=143	300 IR (4M) N=136	100 IR (4M) N=142	Placebo N=148	**Total N=569**	300 IR (4M) N=210	Placebo N=228	**Total N=438**	300 IR (4M) N=131	Placebo N=135	**Total N=266**	300 IR (4M) N=188	300 IR (2M) N=188	Placebo N=205	**Total N=581**
Gender [n (%)]															
Female	54 (37.8)	62 (45.6)	69 (48.6)	60 (40.5)	**245 (43.1)**	109 (51.9)	125 (54.8)	**234 (53.4)**	45 (34.4)	50 (37.0)	**95 (35.7)**	66 (35.1)	77 (41.0)	83 (40.5)	**226 (38.9)**
Male	89 (62.2)	74 (54.4)	73 (51.4)	88 (59.5)	**324 (56.9)**	101 (48.1)	103 (45.2)	**204 (46.6)**	86 (65.6)	85 (63.0)	**171 (64.3)**	122 (64.9)	111 (59.0)	122 (59.5)	**355 (61.1)**
Age (years)															
Mean (SD)	30.4 (7.45)	28.7 (7.34)	29.3 (6.90)	29.1 (7.60)	**29.4 (7.34)**	36.8 (11.27)	37.6 (11.64)	**37.2 (11.46)**	10.5 (3.34)	11.2 (3.07)	**10.9 (3.22)**	30.9 (8.25)	30.4 (7.57)	30.2 (8.56)	**30.5 (8.14)**
Range	18 – 45	18 – 45	18 – 45	18 – 45	**18 – 45**	18 – 65	18 – 65	**18 – 65**	4 – 17*	5 – 17	**4 – 17**	18 – 49	18 – 51	18 – 49	**18 – 51**
BMI (kg/m²)															
Mean (SD)	24.0 (3.91)	24.5 (4.13)	23.8 (3.59)	23.7 (3.54)	**24.0 (3.80)**	27.8 (5.83)	28.5 (5.75)	**28.2 (5.80)**	18.4 (3.27)	19.0 (3.91)	**18.7 (3.62)**	24.3 (3.75)	24.2 (3.62)	24.0 (4.11)	**24.2 (3.84)**
Range	17 – 38	17 – 39	15 – 34	17 – 35	**15 – 39**	16.7 – 48.8	17.3 – 50.7	**16.7 – 50.7**	11 – 27	13 – 37	**11 – 37**	17.2 – 39.0	17.3 – 35.1	15.6 – 42.4	**15.6 – 42.4**
Asth. stat. [n (%)]															
Presence	15 (10.5)	15 (11.0)	14 (9.9)	13 (8.8)	**57 (10.0)**	38 (18.3)	50 (21.9)	**88 (20.2)**	28** (21.4)	29** (21.5)	**57 (21.4)**	28 (14.9)	22 (11.7)	32 (15.6)	**82 (14.1)**
Absence	128 (89.5)	121 (89.0)	128 (90.1)	135 (91.2)	**512 (90.0)**	170 (81.7)	178 (78.1)	**348 (79.8)**	103** (78.6)	106** (78.5)	**209 (78.6)**	160 (85.1)	166 (88.3)	173 (84.4)	**499 (85.9)**
Sens.stat. [n (%)]															
Mono-sensitized	65 (45.5)	66 (48.5)	64 (45.1)	63 (42.6)	**258 (45.3)**	44 (21.0)	53 (23.2)	**97 (22.1)**	54 (41.2)	55 (40.7)	**109 (41.0)**	74 (39.4)	78 (41.5)	81 (39.5)	**233 (40.1)**
Poly-sensitized	78 (54.5)	70 (51.5)	78 (54.9)	85 (57.4)	**311 (54.7)**	166 (79.0)	175 (76.8)	**341 (77.9)**	77 (58.8)	80 (59.3)	**157 (59.0)**	114 (60.6)	110 (58.5)	124 (60.5)	**348 (59.9)**
RC duration (years)															
Mean (SD)	12.1 (8.25)	12.7 (8.12)	11.8 (7.24)	12.1 (8.30)	**12.2 (7.98)**	22.3 (12.77)	23.4 (12.80)	**22.9 (12.78)**	4.6 (2.55)	4.8 (2.49)	**4.69 (2.52)**	13.7 (9.08)	13.8 (8.66)	13.7 (9.46)	**13.8 (9.07)**
Range	1.6 – 40.0	2.0 – 41.1	2.2 – 33.0	2.5 – 41.0	**1.6 – 41.1**	2 – 61	3 – 59	**2 – 61**	1.6 – 16.1	1.6 – 12.1	**1.6 – 16.1**	1.5 – 42.1	1.5 – 39.0	1.6 – 46.1	**1.5 – 46.1**
RRTSS															
Mean (SD)	14.2 (1.77)	14.1 (1.86)	14.2 (1.71)	14.2 (1.68)	**14.2 (1.75)**	14.9 (1.95)	14.9 (1.91)	**14.9 (1.93)**	14.0 (1.67)	14.0 (1.65)	**14.0 (1.66)**	14.1 (1.67)	13.9 (1.75)	14.1 (1.76)	**14.0 (1.73)**
Range	12 – 18	12 – 18	12 – 18	12 – 18	**12 – 18**	12 – 18	12 – 18	**12 – 18**	12 – 18	12 – 18	**12 – 18**	12 – 18	12 – 18	12 – 18	**12 – 18**
Race [n (%)]															
White/Caucasian	ND	ND	ND	ND	**ND**	188 (89.5)	207 (90.8)	**395 (90.2)**	ND	ND	**ND**	ND	ND	ND	**ND**
Black or African American	ND	ND	ND	ND	**ND**	12 (5.7)	15 (6.6)	**27 (6.2)**	ND	ND	**ND**	ND	ND	ND	**ND**
Asian	ND	ND	ND	ND	**ND**	5 (2.4)	0 (0.0)	**5 (1.1)**	ND	ND	**ND**	ND	ND	ND	**ND**
American Indian or Alaska Native	ND	ND	ND	ND	**ND**	0 (0.0)	2 (0.9)	**2 (0.5)**	ND	ND	**ND**	ND	ND	ND	**ND**
Native Hawaiian or Other Pacific Islander	ND	ND	ND	ND	**ND**	0 (0.0)	0 (0.0)	**0 (0.0)**	ND	ND	**ND**	ND	ND	ND	**ND**
Other	ND	ND	ND	ND	**ND**	5 (2.4)	4 (1.8)	**9 (2.1)**	ND	ND	**ND**	ND	ND	ND	**ND**
Ethnicity [n (%)]															
Hispanic or Latino	ND	ND	ND	ND	**ND**	5 (2.4)	3 (1.3)	**8 (1.8)**	ND	ND	**ND**	ND	ND	ND	**ND**

Source: Original BLA application 125471/000 ISE page 58-confirmed by reviewer

7.1.4 Analysis of Primary Endpoint(s)

Considering the results of the primary and secondary analysis (depending on the study examined), it can be seen that when comparing the study treatment at a dose of 300 IR to placebo, the study treatment group had a lower point estimate of CS than placebo.

The primary efficacy endpoint (dependent variable), CS score, was analyzed using a linear model, specifically an ANCOVA with treatment as main effect, pooled study center as stratification factor for the multicenter studies, and several covariates (including: age, gender, baseline symptom/rescue medication scores-depending on the study) which could potentially impact the clinical score. It is important to note that each study utilized its own statistical model that was pre-specified in the protocol rather than a common model for all the studies. The table below summarizes the difference in LSMeans (and 95% CI) of the treated group versus placebo as well as the relative LSMean difference (and 95% CI) utilizing the CS endpoint for all 4 field studies. The results demonstrate that the treatment (particularly the dosage proposed of 300 IR) reduces the CS score when compared to placebo based on both the point estimate of the difference as well as the 95% CI considering the LSMeans values.

Table 7.1.4.a. Repeated Measures ANCOVA of the daily CS Summary of Endpoints based on Protocols submitted by Stallergenes and considered for the Integrated Study of Efficacy-ITT

VO34.04[b, d]							
			Difference in LS Means *vs.* Placebo			Relative LS Mean difference (%)	
Treatment	**n**	**LS Mean**	**Point estimate**[a]	**[95% CI]**	**p-value**	**Point estimate**[a]	**[95% CI]**
500 IR (4M)	143	0.56	-0.14	[-0.23; -0.05]	0.0034	-20.0%	[-33.3%; -6.6%]
300 IR (4M)	136	0.50	-0.21	[-0.30; -0.11]	<0.0001	-29.6%	[-43.1%; -16.1%]
100 IR (4M)	142	0.68	-0.03	[-0.12; 0.07]	0.5769	-3.8%	[-17.2%; 9.6%]
Placebo	148	0.70					
VO61.08USA[b]							
			Difference in LS Means *vs.* Placebo			Relative LS Mean difference (%)	
Treatment	**n**	**LS Mean**	**Point estimate**[a]	**[95% CI]**	**p-value**	**Point estimate**[a]	**[95% CI]**
300 IR (4M)	208	0.32	-0.13	[-0.19; -0.06]	0.0003	-28.2%	[-43.4%; -13.0%]
Placebo	228	0.45					
VO52.06[b, d]							
			Difference in LS Means *vs.* Placebo			Relative LS Mean difference (%)	
Treatment	**n**	**LS Mean**	**Point estimate**[a]	**[95% CI]**	**p-value**	**Point estimate**[a]	**[95% CI]**
300 IR (4M)	131	0.44	-0.19	[-0.29; -0.08]	0.0005	-30.1%	[-46.9%; -13.2%]
Placebo	135	0.63					
VO53.06 Year 1[c, d]							
			Difference in LS Means *vs.* Placebo			Relative LS Mean difference (%)	
Treatment	**n**	**LS Mean**	**Point estimate**[a]	**[95% CI]**	**p-value**	**Point estimate**[a]	**[95% CI]**
300 IR (4M)	188	0.56	-0.11	[-0.18; -0.04]	0.0024	-16.4%	[-27.0%; -5.8%]
300 IR (2M)	188	0.53	-0.14	[-0.21; -0.07]	0.0001	-20.7%	[-31.3%; -10.1%]
Placebo	205	0.67					

CI = Confidence Interval; IR = Index of Reactivity; LS = Least Squares; n: Number of evaluable patients for the statistical model
300 IR (4M) = patients received active treatment starting 4 months prior to the pollen season
300 IR (2M) = patients received active treatment starting 2 months prior to the pollen season
[a] Point estimate = LS Means difference between active treatment and placebo

Source: Original BLA application 125471/000 ISE page 55-confirmed by reviewer

A corresponding forest plot is provided in section 5.3.1. within this review. From the tabulations and the forest plot, it can be observed that the studies provided within this BLA suggest there is a consistent trend of a reduction of symptoms in the active treatment group compared to the placebo group.

7.1.5 Analysis of Secondary Endpoint(s)

Although the applicant considered a variety of endpoints in the different studies to be secondary endpoints, when given the opportunity for feedback within the IND phase of studies, the review team within the Agency consistently proposed Rhinoconjunctivitis Symptom Scores (RSS) and Rescue Medication Scores (RMS) to be secondary endpoints. Thus, in this integrated summary of efficacy, these results of the RSS and RMS will be presented for the field/natural exposure studies.

As in the above analysis for the primary CS endpoint, the members of the review team agrees that utilizing the pre-specified ANCOVA model provided within the protocol is considered appropriate for each study and is preferable to using one single post-hoc model for all the studies. However, other models including: treatment group, gender, age, race, baseline scores, geographic region and various other fixed and random effects in the model were examined and similar conclusions and results were observed.

The table below summarizes the difference in LSMeans (and 95% CI) of the treated group versus placebo as well as the relative LSMean difference (and 95% CI) utilizing the RTSS endpoints for all 4 field studies. The results demonstrate that the treatment (particularly the dosage proposed of 300 IR) reduces the RTSS score when compared to

placebo based on both the point estimate of the difference as well as the 95% CI considering the LSMeans values.

Table 7.1.5.a. Repeated Measures ANCOVA of the Daily RTSS Summary of Endpoints based on Protocols submitted by Stallergenes and considered for the Integrated Study of Efficacy-ITT

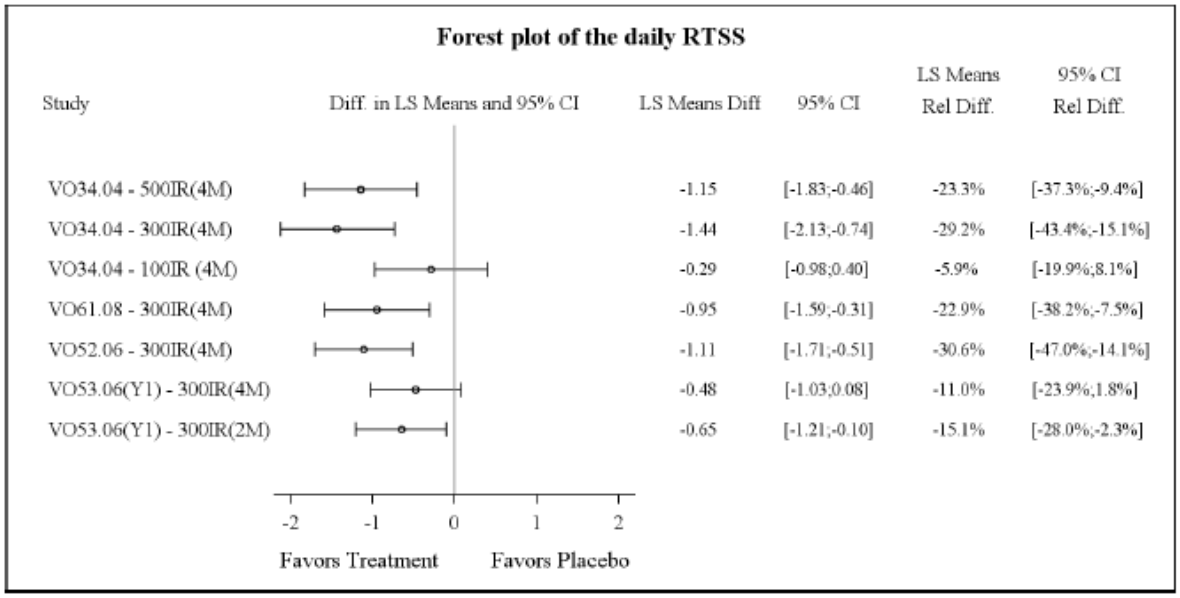
VO34.04[b, d]							
			Difference in LS Means *vs.* Placebo			Relative LS Mean difference (%)	
Treatment	n	LS Mean	Point estimate[a]	[95% CI]	P-value	Point estimate[a]	[95% CI]
500 IR (4M)	143	3.77	-1.15	[-1.83; -0.46]	0.0011	-23.3%	[-37.3%; -9.4%]
300 IR (4M)	136	3.48	-1.44	[-2.13; -0.74]	< 0.0001	-29.2%	[-43.4%; -15.1%]
100 IR (4M)	142	4.62	-0.29	[-0.98; 0.40]	0.4110	-5.9%	[-19.9%; 8.1%]
Placebo	148	4.91					
VO61.08USA[b]							
			Difference in LS Means *vs.* Placebo			Relative LS Mean difference (%)	
Treatment	n	LS Mean	Point estimate[a]	[95% CI]	P-value	Point estimate[a]	[95% CI]
300 IR (4M)	208	3.21	-0.95	[-1.59; -0.31]	0.0036	-22.9%	[-38.2%; -7.5%]
Placebo	228	4.16					
VO52.06[c, d]							
			Difference in LS Means *vs.* Placebo			Relative LS Mean difference (%)	
Treatment	n	LS Mean	Point estimate[a]	[95% CI]	P-value	Point estimate[a]	[95% CI]
300 IR (4M)	131	2.52	-1.11	[-1.71; -0.51]	0.0003	-30.6%	[-47.0%; -14.1%]
Placebo	135	3.63					
VO53.06 Year 1[b, d]							
			Difference in LS Means *vs.* Placebo			Relative LS Mean difference (%)	
Treatment	n	LS Mean	Point estimate[a]	[95% CI]	P-value	Point estimate[a]	[95% CI]
300 IR (4M)	188	3.84	-0.48	[-1.03; 0.08]	0.0911	-11.0%	[-23.9%; 1.8%]
300 IR (2M)	188	3.66	-0.65	[-1.21; -0.10]	0.0209	-15.1%	[-28.0%; -2.3%]
Placebo	205	4.31					

CI = Confidence Interval; IR = Index of Reactivity; LS = Least Squares; n: Number of evaluable patients for the statistical model
300 IR (4M) = patients received active treatment starting 4 months prior to the pollen season
300 IR (2M) = patients received active treatment starting 2 months prior to the pollen season
[a] Point estimate = LS Means difference between active treatment and placebo

Source: Original BLA application 125471/000 ISE page 64-confirmed by reviewer

A forest plot of these values is provided by the applicant and illustrates the effect of the treatment versus placebo difference for RTSS. In the below graph, it is of note that the applicant has included both the 95% CI bars as well as a line denoting a difference of "0." The Agency's preferred clinically meaningful difference is based on the % relative difference of -10%, based on the upper bound of a 95% CI (which can be compared to the final column in the presented values below).

Figure 7.1.5.a. Forest Plot of the Daily RTSS



For completeness and accuracy, the results of all study arms are included in the Figure.
Source: Original BLA application 125471/000 ISE page 65

Comparisons of Rescue Medication Scores based on treatment administered can be seen in the following table and illustrate that again there is a reduction in the rescue medication scores in the 300 IR treated individuals compared to the placebo control individuals.

The table below summarizes the difference in LSMeans (and 95% CI) of the treated group versus placebo as well as the relative LSMean difference (and 95% CI) utilizing the RMS endpoint for all 4 field studies. The results demonstrate that the treatment (particularly the dosage proposed of 300 IR) reduces the RMS score when compared to placebo based on both the point estimate of the difference as well as the 95% CI considering the LSMeans values.

Table 7.1.5.b. Repeated Measures ANCOVA of the daily RMS Summary of Endpoints based on Protocols submitted by Stallergenes and considered for the Integrated Study of Efficacy-ITT

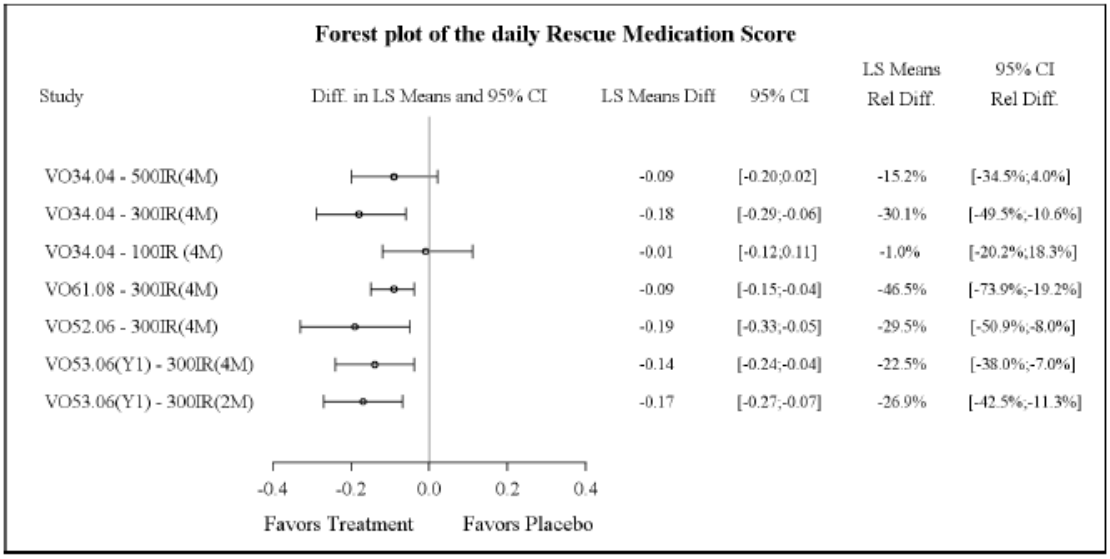
VO34.04[c, d]							
			Difference in LS Means *vs.* Placebo			Relative LS Mean difference (%)	
Treatment	n	LS Mean	Point estimate[a]	[95% CI]	p-value	Point estimate[a]	[95% CI]
500 IR (4M)	143	0.50	-0.09	[-0.20; 0.02]	0.1203	-15.2%	[-34.5%; 4.0%]
300 IR (4M)	136	0.41	-0.18	[-0.29; -0.06]	0.0025	-30.1%	[-49.5%; -10.6%]
100 IR (4M)	142	0.58	-0.01	[-0.12; 0.11]	0.9207	-1.0%	[-20.2%; 18.3%]
Placebo	148	0.59					
VO61.08USA[b]							
			Difference in LS Means *vs.* Placebo			Relative LS Mean difference (%)	
Treatment	n	LS Mean	Point estimate[a]	[95% CI]	p-value	Point estimate[a]	[95% CI]
300 IR (4M)	208	0.11	-0.09	[-0.15; -0.04]	0.0009	-46.5%	[-73.9%; -19.2%]
Placebo	228	0.20					
VO52.06[c, d]							
			Difference in LS Means *vs.* Placebo			Relative LS Mean difference (%)	
Treatment	n	LS Mean	Point estimate[a]	[95% CI]	p-value	Point estimate[a]	[95% CI]
300 IR (4M)	131	0.46	-0.19	[-0.33; -0.05]	0.0071	-29.5%	[-50.9%; -8.0%]
Placebo	135	0.65					
VO53.06 Year 1[b, d]							
			Difference in LS Means *vs.* Placebo			Relative LS Mean difference (%)	
Treatment	n	LS Mean	Point estimate[a]	[95% CI]	p-value	Point estimate[a]	[95% CI]
300 IR (4M)	188	0.49	-0.14	[-0.24; -0.04]	0.0045	-22.5%	[-38.0%; -7.0%]
300 IR (2M)	188	0.46	-0.17	[-0.27; -0.07]	0.0007	-26.9%	[-42.5%; -11.3%]
Placebo	205	0.63					

CI = Confidence Interval; IR = Index of Reactivity; LS = Least Squares; n: Number of evaluable patients for the statistical model
300 IR (4M) = patients received active treatment starting 4 months prior to the pollen season
300 IR (2M) = patients received active treatment starting 2 months prior to the pollen season
[a] Point estimate = LS Means difference between active treatment and placebo

Source: Original BLA application 125471/000 ISE page 67-confirmed by reviewing statistician

A forest plot of these values, provided by the applicant, illustrates the effect of the treatment versus placebo difference for RTSS. This figure applicant shows both the 95% CI of the Difference in LSMeans as well as the relative location with respect to the line denoting "0" or no difference. Also provided are the 95% CIs of the Relative Difference, which can be compared to the Agency's standard for the upper bound of -10%.

Figure 7.1.5.b. Forest Plot of the Daily RTSS



For completeness and accuracy, the results of all study arms are included in the Figure.

Source: Original BLA application 125471/000 ISE page 68

The results and figures included in this section provide evidence that ORALAIR® reduces the use of relief medication (RMS) as well as the symptom score (RTSS) for the LSMeans, utilizing the pre-specified model. This finding is consistent with the results found regarding the primary efficacy endpoint.

7.1.6 Other Endpoints

Analyses of exploratory and additional endpoints have little impact on the evaluation of the product, and thus will not be addressed in the Integrated Analysis of Efficacy. However, other exploratory analyses based on other endpoints including clinical and symptom scores, different analysis sets, and other subset analysis yield similar trends that demonstrate the positive effect of this treatment when compared to placebo.

7.1.7 Subpopulations

Based on the results provided by the applicant and select analyses performed by the reviewing statistician, there do not appear to be significant differences in efficacy between subjects who were mono-sensitized (defined as sensitive to the group of five-grass pollen allergens) and those who were poly-sensitized (also sensitive to cat or dog allergens).

In addition, there were no significant differences in efficacy between: subjects with and without asthma; children and adults; and among subjects who lived in areas with low, medium, or high pollen levels.

For completeness, the following table is presented to provide insight regarding gender effects based on the primary analysis of CS, utilizing the pooled efficacy data. This table summarizes the LSMeans of treatment and placebo as well as the LSMean difference and Relative LS Means difference (and the 95% CI) betweens these groups. These results which were confirmed by the reviewing statistician are presented for females and males.

Table 7.1.7.a. Repeated Measures ANCOVA of the Daily CS in Females and Males during the Pollen Season-ITT Analysis Population

FEMALES							
4-Month Pre-seasonal Pooled Efficacy Analysis[c]							
			Difference in LS Means *vs.* Placebo			Relative LS Mean difference (%)	
Treatment	**n**	**LS Mean**	**Point estimate[a]**	**[95% CI]**	**p-value**	**Point estimate[a]**	**[95% CI]**
300 IR (4M)	281	0.43	-0.15	[-0.21; -0.10]	< 0.0001	-26.2%	[-35.7%; -16.7%]
Placebo	318	0.59					
Heterogeneity test (Treatment by Study Interaction): p = 0.0286							
Adults 4-Month Pre-Seasonal Pooled Efficacy Analysis[c]							
			Difference in LS Means *vs.* Placebo			Relative LS Mean difference (%)	
Treatment	**n**	**LS Mean**	**Point estimate[a]**	**[95% CI]**	**p-value**	**Point estimate[a]**	**[95% CI]**
300 IR (4M)	236	0.47	-0.13	[-0.20; -0.07]	0.0001	-22.3%	[-33.7%; -10.9%]
Placebo	268	0.60					
Heterogeneity test (Treatment by Study Interaction): p = 0.0605, NS							
MALES							
4-Month Pre-seasonal Pooled Efficacy Analysis[c]							
			Difference in LS Means *vs.* Placebo			Relative LS Mean difference (%)	
Treatment	**n**	**LS Mean**	**Point estimate[a]**	**[95% CI]**	**p-value**	**Point estimate[a]**	**[95% CI]**
300 IR (4M)	382	0.37	-0.17	[-0.22; -0.11]	< 0.0001	-31.2%	[-41.1%; -21.3%]
Placebo	398	0.53					
Heterogeneity test (Treatment by Study Interaction): p = 0.9295, NS							
Adults 4-Month Pre-Seasonal Pooled Efficacy Analysis[b]							
			Difference in LS Means *vs.* Placebo			Relative LS Mean difference (%)	
Treatment	**n**	**LS Mean**	**Point estimate[a]**	**[95% CI]**	**p-value**	**Point estimate[a]**	**[95% CI]**
300 IR (4M)	296	0.37	-0.16	[-0.22; -0.10]	< 0.0001	-30.2%	[-41.9%; -18.6%]
Placebo	313	0.53					
Heterogeneity test (Treatment by Study Interaction): p = 0.8840, NS							

CI = Confidence Interval; IR = Index of Reactivity, LS = Least Squares; NS = Not Significant; n: Number of evaluable patients for the statistical model
300 IR (4M) = patients received active treatment starting 4 months prior to the pollen season
[a]Point estimate = LS Means difference between active treatment and placebo

Source: Original BLA application 125471/000 ISE page 96

Based on Table 7.1.7.a, there does not appear to be a difference in response rates or a difference in meeting Agency criteria for efficacy, when comparing males to females utilizing the pooled data.

No subgroup analysis was performed on age or race. A subgroup analysis on age was not performed since the different studies were conducted in different age groups (there was only one pediatric study), and there were no patients 60 years or older. A subgroup analysis on race was not performed since less than 5% of individuals were non-white/Caucasian in any study, and in most studies only white/Caucasian individuals were enrolled.

7.1.10 Additional Efficacy Issues/Analyses

There are no additional efficacy issues or analyses that provide additional insight into the effect of this product. The statistical reviewer did perform additional subset analysis on the applicant provided data to determine if there may have been a specific group that had efficacy results that did not yield similar conclusions regarding the positive effect of this treatment. These subsets included (but are not limited to) baseline skin prick test values, asthma status, dichotomizing based on use of rescue medication, and geographic region. Since this study was not powered to examine these subsets nor were any alpha adjustments made to perform these analysis specific results are not presented; however the trends consistently illustrated that this treatment improves the combined symptom

score and daily medication score. Additionally, this product general appears to reduce the use of rescue medication.

7.1.11 Efficacy Conclusions

The overall results of the efficacy data suggest that there is a reduction of symptoms and use of rescue medication when comparing individuals who were randomized and received 300 IR study treatment compared to individuals who received an indistinguishable placebo product.

The applicant's 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."

Based on the applicant data and analysis which were confirmed by the Agency statistician, this indication appears to be supported.. *However, it is important to note that no study included patients greater than 65 years of age*.

The statistical analyses of the various efficacy studies illustrated that the product reduced the use of rescue medication as well as RTSS, based on LSMeans utilizing pre-specified ANCOVA models. Furthermore, since the Agency consistently recommended a combined score (incorporating both symptoms and rescue medication), regardless of the applicant primary endpoint, this combined score was considered the primary endpoint for the Agency. This issue is particularly relevant to the non-US IND studies, which may have been planned and implemented without Agency input. Since this methodology was consistently recommended and implemented by the Agency, type I error should not be affected.

An additional challenge that was influenced by the non-US-IND studies is the definition of a clinically meaningful endpoint. Several of these studies were designed simply to meet a pre-specified difference and then a p-value less than 0.05. The Agency had a more stringent criterion, requiring the upper bound of the 95% CI of the Relative Difference meeting a clinically meaningful margin of -10%. Many of the non-US studies were not designed or powered for this endpoint. However, it is important to note that several of these studies did meet the US criterion, and other studies demonstrated trends that illustrate the 300 IR treatment group reduces combined scores when compared to the placebo treated group.

Overall, the statistical reviewer agrees with the applicant assertion that ORALAIR® is effective for immunotherapy of ARC due to grass allergy.

8. INTEGRATED OVERVIEW OF SAFETY

8.1 Safety Assessment Methods

The safety methods incorporated a variety of active and passive adverse event reporting mechanisms depending on the study. Subjects were provided daily diary cards in which adverse event symptoms could be noted. Additionally, regular clinic visits were scheduled for the various studies in which subjects were to be asked questions to assess if any symptoms that could be considered adverse events had occurred. All subjects were to be administered the initial dose of Oralair® within a physician's office and observed for a minimum of 30 minutes. During this time frame all individuals were observed and queried for potential symptoms and adverse events. Additional details related to safety assessment methods can be seen in the medical officer and epidemiologists review.

8.2 Safety Database

The safety datasets provided in this submission include the efficacy datasets described in Section 1, as well as the following summary of Safety studies. The table below includes information about each of the safety studies including: the protocol, time of study, study title, study design and objectives, study population, treatment doses and schedule, number of patients exposed and treatment duration.

Table 8.2.a. Summary of Studies that included Safety Information

Protocol #[a]	Completion status Year / pollen season	Location	Study title	Study design, & objectives	Study population Age range	Treatment doses & schedule	Number of exposed patients	Treatment duration
VO33.04 DK	Completed 2004 Out of the pollen season	EU	A Phase I/IIa study to investigate the safety, tolerability and pharmacodynamic effects of SLIT given in single rising doses and in higher multi dose regimens.	DBPC, randomized, single center Safety	Adults with grass-pollen allergic rhinitis 18–50	100 IR to 500 IR Placebo Dose escalation or Direct administration	23[b,d] 7[c,d]	10 days
VO34.04	Completed 2005	EU	Randomised, double-blind, placebo-controlled, multi-national, multi-centre, Phase IIb/III study of the efficacy and safety of three doses of sublingual immunotherapy (SLIT) administered as tablets once daily to patients suffering from grass pollen rhinoconjunctivitis	DBPC, randomized, multi-national multicenter Efficacy, Safety	Adults with grass pollen-related allergic rhino-conjunctivitis 18–45	500 IR (4M) 300 IR (4M) 100 IR (4M) Placebo Dose escalation	160 155 157 156	Approxima-tely 4 months pre-seasonally and ≥ 1 month co-seasonally[a]

DK = Denmark, EU = Europe, DBPC = Double blind placebo controlled, IR = Index of reactivity, SLIT = Sublingual immunotherapy, 4M = patients received active treatment

Source: sBLA 125471/000; Summary of Clinical Safety, Page 10

Table 8.2.b. Summary of Studies that included Safety Information (cont)

Protocol #	Completion status Year / pollen season	Location	Study title	Study design, & objectives	Study population Age range	Treatment doses & schedule	Number of exposed patients	Treatment duration
VO40.05	Early terminated 2006	EU	A randomised, double-blind, placebo-controlled, multi-national, multi-centre, Phase III extension study to assess the long-term efficacy, safety and carry-over effect of one dose of sublingual immunotherapy (SLIT) administered as allergen-based tablets once daily to patients suffering from grass pollen rhinoconjunctivitis	DBPC, randomized, multi-national multicenter Post-treatment efficacy, Safety (Extension of study VO34.04)	Adults with grass pollen-related allergic rhino-conjunctivitis 18-46	300 IR (4M) Placebo Dose escalation	68 25	Approxima-tely 4 months pre-seasonally and ≥ 1 month co-seasonally[e]
VO52.06	Completed 2007	EU	A randomised, double-blind, placebo-controlled, multi-national, multi-centre, Phase III paediatric study of the efficacy and safety of 300 IR sublingual immunotherapy (SLIT) administered as allergen-based tablets once daily to children suffering from grass pollen rhinoconjunctivitis	DBPC, randomized, multi-national multicenter Efficacy, Safety	Children and adolescents with grass pollen-related allergic rhino-conjunctivitis 5-17	300 IR (4M) Placebo Dose escalation	139 139	Approxima-tely 4 months pre-seasonally and ≥ 1 month co-seasonally[e]
VO53.06	Completed 2007 2008 2009 2010 2011	EU, Canada, Russia	A randomised, double-blind, placebo-controlled, multi-national, multi-centre, 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 patients suffering from grass pollen rhinoconjunctivitis	DBPC, randomized, multi-national multicenter Sustained efficacy[f], Post-treatment efficacy, Safety	Adults with grass pollen-related allergic rhino-conjunctivitis 18-50	300 IR (4M) 300 IR (2M) Placebo Direct administration	207 207 219	Approxima-tely 4 months pre-seasonally and ≥ 1 month co-seasonally[e] over 3 years
VO56.07 A	Completed 2007-2008 Out of the pollen season	EU	A randomised, 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	DBPC, randomized, mono-center (allergen exposition chamber study) Efficacy, Safety	Adults with grass pollen-related allergic rhino-conjunctivitis 18-50	300 IR Placebo Direct administration	45 44	Approxima-tely 4 months
VO60.08	Completed 2009	EU	A randomised, 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 patients suffering from grass pollen rhinoconjunctivitis (with or without asthma)	DBPC, randomized, multi-national multicenter Efficacy, Safety	Adults and adolescents with grass pollen-related allergic rhino-conjunctivitis 12-65	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)	Approxima-tely 2 months pre-seasonally and ≥ 1 month co-seasonally[e]
VO61.08 USA	Completed 2009	USA	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 patients suffering from grass pollen rhinoconjunctivitis	DBPC, randomized, multicenter Efficacy, Safety	Adults with grass pollen-related allergic rhino-conjunctivitis 18-65	300 IR (4M) Placebo Direct administration	233 240	Approxima-tely 4 months pre-seasonally and ≥ 1 month co-seasonally[e]

A = Austria, EU = Europe, DBPC = Double-blind placebo-controlled, IR = Index of reactivity, SLIT = Sublingual immunotherapy, 4M = patients received active treatment starting 4 months prior to the pollen season, 2M = patients received active treatment starting 2 months prior to the pollen season.
[e] Depending on the start and duration of the pollen season and the planned visit date.
All clinical study reports are available in Module 5 Section 5.3.5.1 (VO34.04, VO52.06, VO53.06, VO56.07A, VO60.08 and VO61.08USA) and Section 5.3.5.4 (VO33.04DK and VO40.05) of this application.

Source: sBLA 125471/000; Summary of Clinical Safety, Page 10

The following summarizes the extent of exposure to any treatment (including placebo and dosages of Oralair® not submitted for consideration in this BLA) in all studies provided within this BLA. This table includes the number of patients, mean exposure and range of exposure for adults as well as children and adolescents.

Table 8.2.c. Extent of Exposure of All Subjects

	ALL PATIENTS			
	500 IR	**300 IR**	**100 IR**	**Placebo**
Number of patients (n)	177	1180	157	998
Mean exposure (Days)	158.8	214.5	178.4	212.0
Range of exposure (Days)	1 – 245	0[a] – 597	15 – 239	1 – 596
	ADULTS			
	500 IR	**300 IR**	**100 IR**	**Placebo**
Number of patients (n)	177	1026	157	840
Mean exposure (Days)	158.8	224.2	178.4	223.0
Range of exposure (Days)	1 – 245	0[a] – 597	15 – 239	1 – 596
	CHILDREN AND ADOLESCENTS			
	500 IR	**300 IR**	**100 IR**	**Placebo**
Number of patients (n)	-	154	-	158
Mean exposure (Days)	-	149.9	-	153.2
Range of exposure (Days)	-	12 – 197	-	21 – 196

IR = Index of reactivity

Note: Participants in studies which included dose escalation (i.e., VO33.04DK, VO34.04 and VO52.06) were attributed to the maximum dose to which they were exposed. Specifically, 12 participants were exposed to 100 IR and 300 IR before receiving 500 IR. In this table, these participants are included under the 500 IR dose.

[a] In study VO53.06, five patients randomized to the 300 IR (2M) group withdrew during the period when they were receiving placebo (i.e., before any intake of active treatment).

Source: sBLA 125471/000; Summary of Clinical Safety, Page 17

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

The demographics of the safety database based on the treatment groups were provided by the applicant and confirmed by the reviewing statistician via JMP. The results of the tabulations of the pooled exposure to treatment or placebo can be seen from the below table. This table includes the sample size (n) and percentage of individuals for the Safety Analysis set based on age, gender, height, weight and BMI stratified by treatment group. Overall the demographics appear to be similar between the treatment groups when pooling all the studies that collected safety data; however, as can be seen in the below table it is of note that there are slightly more males (57% and 55% for the active and placebo treated groups, respectively), in this study than females.

Table 8.2.2.a. Summary of Demographic Characteristics-Safety Analysis Set-All doses in All Studies

	ALL PATIENTS, ALL DOSES	
	Active N=1514	**Placebo** N=998
Gender [n (%)]		
Male	870 (57.5)	551 (55.2)
Female	644 (42.5)	447 (44.8)
Age (years)		
Mean (SD)	29.0 (10.48)	28.8 (11.89)
Range	4 – 65	5 – 65
BMI (kg/m^2)		
Mean (SD)	24.1 (4.68)	24.4 (5.31)
Range	11 – 49	13 – 51
Asthma status [n (%)]		
Presence	242 (16.0)	183 (18.3)
Absence	1270 (84.0)	815 (81.7)
Sensitization status [n (%)]		
Mono-sensitized	587 (38.8)	364 (36.5)
Poly-sensitized	927 (61.2)	633 (63.5)
Rhinoconjunctivitis duration (years)[a]		
Mean (SD)	13.6 (9.92)	14.2 (11.03)
Range	2 – 61	2 – 59

N = Number of patients per treatment group, n = number of patients, SD = Standard deviation, BMI = Body mass index.
[a] Data were not available for participants in study VO33.04DK (23 actively-treated patients and 7 placebo-treated patients)
Source: sBLA 125471/000; Summary of Clinical Safety, Page 36

The following table further explores the demographics of the safety database of adults 18 years of age and greater within the study based on the treatment groups were provided by the applicant and confirmed by the reviewing statistician via JMP. The results of the tabulations of the pooled exposure to treatment or placebo can be seen from the below table. This table includes the sample size (n) and percentage of individuals for the Safety Analysis set based on age, gender, height, weight and BMI stratified by treatment group. Similar trends and patterns are observed in the full safety database including all individuals are noted when considering only adult subjects as can seen in the table below.

Table 8.2.2.b. Summary of Demographic Characteristics-Safety Analysis Set-300 IR Doses from All Studies

	ADULTS, 300 IR	
	Active N=1038	**Placebo** N=840
Gender [n (%)]		
Male	583 (56.2)	451 (53.7)
Female	455 (43.8)	389 (46.3)
Age (years)		
Mean (SD)	31.5 (9.39)	32.1 (9.99)
Range	18 – 65	18 – 65
BMI (kg/m^2)		
Mean (SD)	25.0 (4.56)	25.3 (4.99)
Range	17 – 49	16 – 51
Asthma status [n (%)]		
Presence	179 (17.3)	149 (17.7)
Absence	857 (82.7)	691 (82.3)
Sensitization status [n (%)]		
Mono-sensitized	375 (36.1)	301 (35.9)
Poly-sensitized	663 (63.9)	538 (64.1)
Rhinoconjunctivitis duration (years)		
Mean (SD)	15.5 (10.38)	15.9 (11.18)
Range	2 – 61	2 – 59

IR = Index of reactivity, N = Number of patients per treatment group, n = number of patients, SD = Standard deviation, BMI = Body mass index.

Source: sBLA 125471/000; Summary of Clinical Safety, Page 37

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

Since these studies were performed in a variety of locations and under different INDs (some non-US INDs) the caution should be used when interpreting results. However, considering the results and trends were consistent regardless of studies this may be less of a concern than if different conclusions were made depending on the individual study.

8.4 Safety Results

A summary of the adverse events can be seen in the table below. Based on the tabulated values similar trends of adverse events can be seen in both the treatment and placebo treated patients (78% and 71% respectively). The table below provides a brief description of the adverse event, the count and % of observed subjects with the Adverse Event stratified by treatment group. It is important to note that this table combines all treatment doses of the active treatment.

Table 8.4. Overview of Adverse Events-Safety Analysis Set-All Doses from All Studies

Description	ALL PATIENTS, ALL DOSES	
	Active[a] N=1514 n (%) [m]	**Placebo** N=998 n (%) [m]
At least one AE	1178 (77.8) [6591]	713 (71.4) [3104]
At least one non-TEAE	283 (18.7) [732]	196 (19.6) [493]
At least one TEAE	1164 (76.9) [5859]	697 (69.8) [2611]
At least one drug-related AE	881 (58.2) [2960]	202 (20.2) [364]
At least one drug-related non-TEAE	4 (0.3) [5]	3 (0.3) [4]
At least one drug-related TEAE	880 (58.1) [2955]	200 (20.0) [360]
AE leading to death	0 (0.0) [0]	0 (0.0) [0]
At least one serious AE	32 (2.1) [37]	18 (1.8) [24]
At least one serious non-TEAE	11 (0.7) [11]	7 (0.7) [10]
At least one serious TEAE	22 (1.5) [26]	11 (1.1) [14]
At least one serious drug-related AE	3 (0.2) [3]	0 (0.0) [0]
At least one serious drug-related non-TEAE	0 (0.0) [0]	0 (0.0) [0]
At least one serious drug-related TEAE	3 (0.2) [3]	0 (0.0) [0]
AE leading to premature study withdrawal	81 (5.4) [89]	12 (1.2) [12]
Non-TEAE leading to premature study withdrawal	4 (0.3) [4]	0 (0.0) [0]
TEAE leading to premature study withdrawal	77 (5.1) [85]	12 (1.2) [12]

N = Number of patients per treatment group, n = Number of patients reporting an AE, % = Percentage of patients reporting an AE, m = number of mentions of events, AE = Adverse event, TEAE = Treatment-emergent adverse event
An individual patient could have reported more than one episode of an adverse event, but contributed only once.
[a] Of note, 207 patients (300 IR [2M] group in study VO53.06) received placebo for 2 months before starting active treatment.
Source: Module 5 Section 5.3.5.3.2 *Appendix 1 Table P1.4*

Considering treatment emergent adverse events listed in the table above, the treated group had a greater likelihood of TEAEs with 58% versus 20% when comparing the treatment group to the placebo treated individuals. Additional comments related to global AEs for the pooled results can be seen in the Medical Officer and Epidemiologists reviews.

8.4.1 Deaths

No deaths were reported in any studies submitted by the applicant.

8.4.2 Nonfatal Serious Adverse Events

Limited non-fatal serious Adverse Events were reported. Within all studies there were 32 (2.1%) serious adverse events in the treated group while there were 18 (1.8%) serious adverse events in the placebo group. All serious adverse events were noted to be self-limiting and resolved. Additional details can be found in the medical reviewer's and epidemiologist's review.

8.4.3 Study Dropouts/Discontinuations

Within all studies submitted by the applicant approximately 5% of treated subjects and approximately 1% of placebo treated subjects discontinued treatment. The reason for discontinuation varied but the predominant reason for drop out were local side effects including swelling and irritation in the mouth/tongue and oral region. A detailed discussion related to dropouts and discontinuations is deferred to the medical officer and epidemiologists.

8.4.4 Common Adverse Events

The majority of adverse events that were observed and noted within the various studies were related to allergies (i.e., rhinoconjunctivitis symptoms) for both active treated and placebo treated patients. Overall, approximately 77% and 70% of subjects in the treatment and placebo groups, respectively, experienced adverse events. The majority of these adverse events were local reactions that involved the throat, nasal and oral region as well as the GI tract, which is to be expected when considering grass allergic individuals with symptoms noted at baseline. Further discussion and details related to common adverse events is deferred to the medical officer and epidemiologist.

8.4.5 Clinical Test Results

Clinical test results varied between and within the studies. However, endpoints including IgG, IgE, and other tests performed had results that were expected and not considered outside of normal ranges.

8.4.6 Systemic Adverse Events

There were no episodes of anaphylaxis or anaphylactic shock observed in any subjects within the submitted studies. Rarely (less than 1% of individuals) uticaria and systemic rashes were observed. Additional details related to systemic adverse events can be found in the medical officer's review.

8.4.7 Local Reactogenicity

There were local reactions noted in both the treated as well as placebo treated individuals (77% and 70% respectively). The majority of these adverse reactions were either gastro-intestinal or were irritation located in the administration site: the throat. The majority of these events were mild or moderate and all were self-limiting. Additional details related to systemic adverse events can be found in the medical officer's review.

8.4.8 Adverse Events of Special Interest

No adverse events of special interest were noted in the submitted studies.

8.5 Additional Safety Evaluations

Although this product had adverse events noted, these were to be expected since this product is composed of the allergen the individuals are allergic to. All issues associated with adverse events that were noted were self-limiting and resolved by study completion.

8.5.1 Dose Dependency for Adverse Events

In the studies provided, the applicant 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 AEs than the 100 IR dose. To ensure optimal performance, the applicant selected the 300 IR dose to maximize the safety benefit profile of this product.

8.5.2 Time Dependency for Adverse Events

The timing of the adverse events varied from minutes of administration to days/weeks after initial dose (but during daily dosing regimen). The severe adverse events were typically noted in the first day of treatment (within minutes), while the individual was under the care of the physician within a medical office setting. All adverse events noted in the first day of treatment resolved. The adverse events that occurred later in time tended to be gastrointestinal in nature and also were self-limiting. Additional comments can be seen in the Medical Officer's and Epidemiologist's Review.

8.6 Safety Conclusions

Based on the observed safety data including AEs this product frequently causes local AEs in the oral region that are known to be associated with SLIT (since it is administered by mouth). The data reviewed support the general conclusion that the incidence of severe or serious AE associated with SLIT is non-life-threatening and self-limiting. Additional details can be seen in the Medical Officer's and Epidemiologist's Reviews.

9. ADDITIONAL STATISTICAL ISSUES

No additional statistical issues were noted during the examination and re-analysis of the efficacy and safety data provided by the applicant.

9.1 Special Populations

No special populations were examined in any studies submitted within this BLA.

9.1.1 Human Reproduction and Pregnancy Data

There are no data regarding human reproduction or pregnancy provided within this submission.

9.1.2 Use During Lactation

There are no data regarding the use of this product in lactating individuals provided within this submission.

9.1.3 Pediatric Use and PREA Considerations

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. Additionally, 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. No children under 5 years of age were observed in any of the studies submitted by the applicant.

9.1.4 Immunocompromised Patients

There are no data regarding individuals with compromised immunity provided within this submission particularly since immunocompromised subjects were excluded from the studies.

9.1.5 Geriatric Use

There are no data regarding geriatric use in individuals older than 65 years of age provided within any studies submitted by the applicant.

9.2 Aspect(s) of the Statistical Evaluation Not Previously Covered

The reviewer has no additional comments.

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

The studies provided in this submission appear to support the applicant conjecture that the Oralair® 300 IR product is safe and effective in the treatment of allergic rhinoconjunctivitis, using the Agency's pre-specified criterion for efficacy based on the Combined Symptom score that incorporates both rescue medication and symptom scores.

10.2 Conclusions and Recommendations

Based on the data submitted and reviewed, ORALAIR®, 300 IR per dose, appears to be safe and effective for immunotherapy of allergic rhinoconjunctivitis due to sensitivity to any combination of the five grass pollens included in the product. The product appears to be safe and effective for adults 10-65 years of age, based on the statistical analyses examined and performed by the reviewing statistician.