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Application Type	BLA Efficacy Supplement
STN	125471/230
CBER Received Date	January 11, 2018
PDUFA Goal Date	November 11, 2018
Division / Office	DVRPA/OVRR
Committee Chair	Kelsey Hoffman
Clinical Reviewer	Joohee Lee
Project Managers	Kamalakannan Velmurugan; Tatiana Clarodasilva
Priority Review	No
Reviewer Name	Jennifer L. Kirk, Ph.D.
Review Completion Date / Stamped Date	
Supervisory Concurrence	Lihan Yan, Ph.D. Team Leader, Bacterial & Allergenic Product Team
	Tsai-Lien Lin, Ph.D. Chief, Vaccine Evaluation Branch/DB/OBE
Applicant	Stallergenes, SAS
Established Name	Sweet Vernal, Orchard, Perennial Rye, Timothy and Kentucky Blue Grass Mixed Pollens Allergen Extract
Trade Name	ORALAIR
Pharmacologic Class	Allergenic
Formulation(s), including Adjuvants, etc	Sweet Vernal, Orchard, Perennial Rye, Timothy and Kentucky Blue Grass Mixed Pollens Allergen Extract
Dosage Form(s) and Route(s) of Administration	100IR and 300IR Tablets for Sublingual Use
Dosing Regimen	Tablets, 100 and 300 IR (index of reactivity)

Indication(s) and Intended Population(s)	Treatment of grass pollen-induced allergic rhinitis with or without conjunctivitis confirmed by positive skin test or in vitro testing for pollen-specific IgE antibodies for any of the five grass species contained in this product for use in persons 10 through 65 years of age

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1. Executive Summary

ORALAIR is a sublingual immunotherapy tablet manufactured by Stallergenes S. A. which contains allergenic extracts from 5 grass species. ORALAIR was approved in 2014 for the treatment of grass pollen-induced allergic rhinitis with or without conjunctivitis for any of the five grass species in persons 10 through 65 years of age. At the time of approval, the Allergenic Product Advisory Committee voted that there was sufficient evidence of efficacy but insufficient safety data in children aged 5 to 9 years old. The original approval letter contained a post-marketing commitment to study ORALAIR in children aged 5 to 9 years old.

In this efficacy supplement, the applicant submitted the results of a post-marketing study in children aged 5 to 9 years old, along with a post-hoc reanalysis of the single pediatric study (VO52.06) from the original Biologics Licensing Application (BLA). This memo provides a review of the post-hoc reanalysis only.

Study VO52.06 was a multi-national, multicenter, randomized, placebo-controlled, double-blind natural field study of ORALAIR conducted in 30 European countries. The primary objective of the study was to demonstrate the efficacy of VO52.06 as measured by the Rhinoconjunctivitis Total Symptom Score (RTSS). A total of 278 children aged 5 to 17 years old were randomized 1:1 to ORALAIR or placebo. Subjects started treatment 4 to 5 months before the start of the pollen season and treatment continued through the end of the pollen season. Subjects recorded daily symptom scores throughout the pollen season.

The primary efficacy analysis, presented in the original BLA, estimated the treatment effect on the average RTSS score during the pollen season. Using a model adjusted for gender, asthma, grass sensitization status, and pooled center, the difference between ORALAIR and placebo in the average RTSS with 95% confidence interval (CI) was −1.13 (95% CI: −1.80, −0.46) or a −28.0% difference relative to placebo. In the integrated summary of efficacy from the original BLA, a post-hoc analysis of the daily Combined Score (CS) was performed using a repeated measures analysis of covariance (ANCOVA) model adjusted for pooled center, age, gender, asthma, grass sensitization status, and the number of days since the start of the pollen season. The difference in the daily CS between ORALAIR and placebo was −0.19 (95% CI: −0.29, −0.08) or a −30.5% difference relative to placebo.

In this supplement, the applicant submitted a post-hoc analysis of the daily CS using a repeated measures ANCOVA model that was adjusted for pooled center, age group, gender, asthma, and grass sensitization status with an interaction term for treatment by age group (5–11, 12–17 years old). This analysis found no significant difference between the efficacies of ORALAIR in the two age groups.

CBER requested a post-hoc analysis of the daily CS for subjects aged 5–9 years old and 10–17 years old separately. This subgroup analysis used the same repeated measures ANCOVA model as in the post-hoc analysis submitted in the original BLA for the

integrated summary of efficacy. Based on this analysis, the difference in daily CS was −0.26 (95% CI: −0.45, −0.06) for children 5–9 years old and −0.14 (95% CI: −0.27, −0.01) for children 10–17 years old, which are equivalent to −34.7% (−61.6%, −7.7%) and −24.4% (−51.6%, 2.9%) differences from placebo, respectively. The results for daily RTSS for children aged 5–9 years old met the pre-specified success criteria of an upper 95% confidence interval less than −10%, but the results for daily CS and Rescue Medication Score (RMS) did not. The results of this analysis suggest numerically similar or higher efficacy for children aged 5−9 years old compared to the other age subgroups. However, these post-hoc results are based on a small sample size and subjects were not randomized within these age subgroups. Therefore, these analyses may be underpowered and subject to residual confounding.

2. Clinical and Regulatory Background

ORALAIR is a sublingual immunotherapy tablet (SLIT) manufactured by Stallergenes S. A. that contains allergenic extracts from Sweet Vernal, Orchard, Perennial Rye, Timothy, and Kentucky Blue Grass pollens. ORALAIR was approved in 2014 for the treatment of grass pollen-induced allergic rhinitis with or without conjunctivitis confirmed by positive skin test or in vitro testing for pollen-specific IgE antibodies for any of the five species of grass contained in the product. ORALAIR is approved for use in people aged 10 to 65 years old.

In the original biologics licensing application (BLA), Stallergenes submitted two pediatric studies, VO60.08 and VO52.06. VO60.08 was a randomized, placebo-controlled study of ORALAIR in adolescents and adults aged 12 to 65 years old. VO60.08 found no significant difference between ORALAIR and placebo for the primary efficacy endpoint and was not used to establish efficacy, but did contribute to the safety assessment. VO52.06 was a randomized natural field study conducted in European children and adolescents that found a significant treatment effect for ORALAIR compared to placebo.

On December 11, 2013, the Allergenic Product Advisory Committee (APAC) was convened to answer several questions about the ORALAIR original BLA:

1. Do the available data support the efficacy of ORALAIR for the treatment of grass pollen-induced allergic rhinitis or conjunctivitis in persons five years of age or older, when administered prior to and during the grass pollen season? Please vote yes or no.
2. Are the available data adequate to support the safety of ORALAIR when administered to persons five years of age or older? In your deliberations, please consider the available safety data for children and adolescents, adults, and the elderly. Please vote yes or no.
3. Please discuss whether the available data support the continued efficacy of ORALAIR through 1 and 2 years following courses of treatment for the previous three grass pollen seasons.
4. Please comment on what additional studies, if any, should be conducted post-licensure.

During APAC deliberations, several committee members expressed concerns about the criteria for, distribution of, and communication of rare but serious systemic adverse events, such as anaphylaxis. Committee members also expressed safety concerns related to adherence and dosing, as well as safety for patients with persistent asthma. Concerns specific to the pediatric population included a lack of safety data in younger children, treatment adherence among younger children, and the potential for increased adverse events for patients experiencing fever, especially for the youngest children.

For question 1, 9 members voted yes and 1 member voted no. The single no vote was caused by the lack of age qualification (5 to 65 years) in the question. For question 2, 5 members voted yes, 4 members voted no, and one member abstained. Committee members voting no for question 2 cited a lack of data about asthmatics, persons older than 65, and children, especially those 9 years old and younger.

In response to the committee's strong opinions about question 2, CBER posed a revised question 2 with two parts, which were drafted at the meeting:

A. Are the available data adequate to support the safety of ORALAIR when administered to persons 5 through 9 years of age?
B. Are the available data adequate to support the safety of ORALAIR when administered to persons 10 through 65 years of age?

For question 2A, 5 members voted yes and 5 members voted no. Committee members voted no because of a lack of data, not because of a specific safety concern. For question 2B, the vote was unanimously yes.

In response to question 4, committee members mentioned several adverse events and patient populations for which they desired more post-marketing data, including children aged 5 to 10 years old. Committee members were concerned about the safety in this pediatric population and may have been concerned about efficacy as well.

On April 1, 2014, ORALAIR was approved for the treatment of grass pollen induced allergic rhinitis with or without conjunctivitis confirmed by positive skin test or in vitro testing for pollen-specific IgE antibodies for any of the five grass species contained in the product in persons aged 10 through 65 years of age. In the approval letter, the pediatric requirement for children aged less than 5 years old was waived and the requirement for children aged 5 to less than 10 years old was deferred, with a post-marketing commitment of a single pediatric study in children aged 5 to less than 10 years old (Study 140224). No purpose was designated for this pediatric study in the approval letter.

The protocol for the post-marketing pediatric study (Study SL74.14) was first submitted to IND 13776/98 with subsequent revisions. This study was a multicenter observational study in children aged 5 to 9 years old of the safety and tolerability of ORALAIR as measured in 30 days of treatment.

This submission includes the results from the pediatric study SL74.14, along with a post-hoc analysis of the VO52.06 data to support efficacy in children aged 5 to 9 years old. The focus of this statistical review is the post-hoc analysis of the VO52.06 data. Study SL74.14 is reviewed by the medical officer.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

In general, the quality of the submission was acceptable.

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

Not applicable.

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

This review refers to the following documents from the original BLA submission (STN 125471/0):

- VO52.06 Clinical Study Report, which includes the protocol and SAP
- STN 125471/0 5.3.5.3.1 Integrated Summary of Efficacy
- STN 125471/0 Statistical Review Memo

the following document from this supplement (STN 125471/230.0):

- 2.5 Addendum to Clinical Overview

the two responses to information requests:

- STN 125471/230.2 Response to FDA email dated 23 March 2018
- STN 125471/230.2 Repeated Measures Ancova of the daily Combined Score in 5–9 years old ITT Population
- STN 125471/230.2 Repeated Measures Ancova of the daily Combined Score in 10–17 years old ITT Population
- STN 125471/230.2 Repeated Measures Ancova of the daily Rhinonconjuncivitis Total Symptom Score in 5–9 years old ITT Population
- STN 125471/230.2 Repeated Measures Ancova of the daily Rhinonconjuncivitis Total Symptom in 10–17 years old ITT Population
- STN 125471/230.2 Repeated Measures Ancova of the daily Rescue Medication Score in 5–9 years old ITT Population
- STN 125471/230.2 Repeated Measures Ancova of the daily Rescue Medication Score in 10–17 years old ITT Population
- STN 125471/230.3 Response to FDA email date 21 June 2018

and the following other documents:

- December 11, 2013 Advisory Committee Meeting Transcript

- April 1, 2014 Original BLA Approval Letter
- ORALAIR Package Insert (as of August 8, 2018)

The datasets and corresponding documentation used in this analysis include the following datasets from STN 125471/230.2:

- dm_dd
- ef_dd
- Data Definitions

and the following documentation from the original BLA (STN 125471/0):

- VO52.06 Data Guide
- VO56.02 Data Definition (m5\datasets\VO52.06\analysis\legacy\datasets\define.pdf)
- ISE Data Guide (m5\datasets\ISE\analysis\legacy\datasets\define.pdf)

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 VO52.06

6.1.1 Study Design

VO52.06 was a multi-national, multicenter, randomized, double-blind, placebo-controlled study of the safety and efficacy of ORALAIR in European children aged 5 to 17 years old, inclusive. VO52.06 was a natural field study that was not conducted under IND.

The primary objective of VO52.06 was to assess the efficacy of SLIT for grass pollen allergens as measured by the rhinoconjunctivitis total symptom score (RTSS). The RTSS is defined as the sum of six rhinoconjunctivitis symptom scores: sneezing, rhinorrhea, nasal pruritus, nasal congestion, ocular pruritus, and watery eyes. Each symptom score is measured on a scale from 0, corresponding to no symptoms, to 3, corresponding to severe symptoms. The secondary objectives of VO52.06 were to assess the safety of the treatment and the efficacy of SLIT for grass pollen allergens as measured by:

- rescue medication score and usage,
- the combined score,
- each of the rhinoconjunctivitis symptom scores,
- the proportion of symptom-free days,
- and a global evaluation of the efficacy of SLIT for grass pollen allergens by the patient.

The rescue medication score ranges from 0 to 3. Rescue medication was provided by the study staff and administered using a prespecified stepwise treatment regimen which the rescue medication score parallels: 0 indicates no rescue medication, 1 indicates antihistamines, 2 indicates nasal corticosteroids, and 3 indicates oral corticosteroids. The combined score (CS) is the average of the average RTSS and the RMS. The CS is calculated as $\frac{1}{2}\left(\frac{RTSS}{6} + RMS\right)$ and ranges from 0 to 3. The CS is the preferred measure of

efficacy because many subjects are unable to discontinue rescue medication during the grass pollen season.

VO52.06 recruited children aged 5 to 17 years old who were generally healthy, had grass pollen-related allergic rhinoconjunctivitis for at least two pollen seasons prior to the study start, a positive skin prick test, and a score of at least 12 on the retrospective RTSS (RRTSS). Children were ineligible for the study if they had asthma requiring treatment other than beta-2 inhaled agonists or rhinoconjunctivitis symptoms during the grass pollen season that were caused by allergens other than grass pollen, including perennial allergens.

Approximately 4 to 5 months before the start of the pollen season, subjects were screened for eligibility. At the screening visit, asthma and sensitization status (mono- or poly-sensitized to the grass pollens in ORALAIR) were ascertained, as was the RRTSS. The RRTSS measures the severity of the six rhinoconjunctivitis symptoms during the previous pollen season on the same 0 to 3 point scale as the RTSS. A total of 278 eligible subjects from 28 different sites in 5 different countries were randomized 1:1 to ORALAIR or placebo. Within 4 weeks of randomization, subjects began treatment. Treatment continued until the end of the pollen season. Throughout treatment, safety was assessed, and subjects recorded their daily rhinoconjunctivitis symptom scores.

VO52.06 was powered to detect a difference of 1.2 in the average RTSS score between ORALAIR and placebo during the pollen season with 80% power at a significance level of 0.05. The applicant planned to randomize 140 subjects per treatment group, allowing for 15% dropout during the study.

6.1.2 Original Analysis & Results

The prespecified analysis and results of VO52.06 were reviewed in the original BLA statistical review memo. A brief review of those results is provided to inform the discussion of the post-hoc analyses.

6.1.2.1 Patient Disposition & Demographics

A total of 320 patients were screened, of which, 278 were randomized. The intent-to-treat (ITT) population included 266 subjects, with 135 placebo subjects and 131 ORALAIR subjects. The 12 subjects excluded from the ITT population had no rhinoconjunctivitis symptom scores recorded during the pollen season. The number of subjects per site ranged from 2 to 28. For the efficacy analyses, sites were combined into 13 pooled sites, with 11 to 59 subjects per pooled site.

In the original BLA submission, the applicant provided summary statistics for the intent-to-treat population by treatment group (Table 1). The statistical reviewer for the original BLA confirmed the demographics and noted that the treatment groups were generally balanced, although there were more male children than female children in this study.

Table 1. Intent-to-Treat Population Demographics by Treatment Group

Characteristic		ORALAIR	Placebo
Gender	Female	45 (34.4%)	50 (37.0%)
	Male	86 (65.6%)	85 (63.0%)
Age Group	5–11 years old	82 (62.6%)	71 (52.6%)
	12–17 years old	49 (37.4%)	64 (47.4%)
	Age (years) Mean (SD)	10.5 (3.34)	11.2 (3.07)
	Weight (kg) Mean (SD)	40.9 (15.58)	44.4 (16.63)
	Height (cm) Mean (SD)	146.2 (19.06)	150.1 (17.14)
	Body Mass Index (kg/m^2) Mean (SD)	18.4 (3.27)	19.0 (3.91)

Source: The statistical reviewer created this table based on Table 8 in the VO52.06 study report (p. 58).

Statistical Reviewer's Comment: *I have confirmed the summary statistics presented in Table 1. Because the age range of interest for this efficacy supplement is 5 to 9 years old, I have calculated number and percent of ITT subjects in the 5–9 years old and 10–17 years old age groups.*

Table 2. Intent-to-Treat Population by Age Group

Age Group	ORALAIR	Placebo
5–9 years old	54 (41.2%)	40 (29.6%)
10–17 years old	77 (58.8%)	95 (70.4%)

Source: The statistical reviewer created this table using the VO52.06 dataset dm_dd.

There is a modest imbalance in the age distribution between the treatment and placebo groups. This imbalance is more pronounced using these age groups, compared to the demographics presented by the applicant, because the placebo group tends to be older and therefore has more subjects aged 10–12 years old.

The table below shows the demographics by treatment group for the ITT subjects aged 5–9 years old. The imbalance in males and females is still present and is approximately the same as observed in the full data set. As expected, these younger subjects are shorter and lighter, making the average weight, height, and body mass index (BMI) smaller. The standard deviations are smaller, as well, because children aged 5–9 years old are more similar in height, weight, and BMI than children 5–17 years old. Overall, the two treatment groups are generally balanced within each age group with respect to demographics.

Table 3. Intent-to-Treat 5 to 9 Year Old Population Demographics by Treatment Group

Characteristic		ORALAIR	Placebo
Gender	Female	21 (38.9%)	12 (30.0%)
	Male	33 (61.1%)	28 (70.0%)
Age (years) Mean (SD)		7.3 (1.4)	7.5 (1.3)
Weight (kg) Mean (SD)		28.0 (7.1)	29.1 (7.3)
Height (cm) Mean (SD)		128.4 (9.9)	130.3 (10.8)
Body Mass Index (kg/m^2) Mean (SD)		16.7 (2.5)	17.0 (2.8)

Source: The statistical reviewer created this table using the VO52.06 dataset dm_dd.

6.1.2.2 Primary Efficacy Analysis

The primary efficacy endpoint was the average RTSS (ARTSS) over the grass pollen season. The pollen season was establish using a predefined protocol after the collection of all study data but before the study was unblinded. For each subject, only data from days during the pollen seasons with complete rhinoconjunctivitis symptom scores were used. The ARTSS was calculated for each subject by averaging over all days with complete rhinoconjunctivitis symptom scores during the pollen period.

The treatment effect was assessed using an analysis of covariance (ANCOVA) model adjusted for the pooled center, RRTSS, age, gender, asthma, and grass sensitization status. Gender, asthma, grass sensitization status, and pooled center were included in the model as categorical variables, while age was included as a numeric variable. This adjusted model yielded a difference in ARTSS between the treatment and placebo groups of −1.13 with a 95% confidence interval (CI) of (−1.80, −0.46) and a percent difference relative to placebo of −28.0%. This met the specified success criteria of a 20% or greater decrease in the ARTSS over the grass pollen season.

Statistical Reviewer's Comment: *I have confirmed the results of the primary efficacy analysis using the ef_dd dataset and the specified ANCOVA model in SAS 9.4. No confidence interval for the percent difference from placebo is provided in the original VO52.06 study report. The original statistical review gives the point estimate and 95% confidence interval −25.6% (−40.4%, −10.3%) for the percent difference from placebo. No method is described for these estimates, but using the least-squares means and variances from the ANCOVA model, via the delta method, I estimate a percent difference of −25.5% (95% CI: −41.5%, −9.4%) using* R 3.5.1.

6.1.2.3 Secondary Efficacy Analyses

The secondary efficacy analyses included the average rescue medication score and the average combined score, two measures which are considered more clinically meaningful than the ARTSS. The results for both are presented in Table 4. The treatment effects on the average CS and RMS over the grass pollen season were modeled using the same

ANCOVA model as the primary efficacy analysis (see section 4.2.2). The results of the secondary analysis are generally consistent with the results from the primary analysis.

Table 4. Combined Intent-to-Treat Population Pollen Season Average Combined Score (CS) and Rescue Medication Score (RMS) Treatment Effect with 95% Confidence Intervals (CI)

Endpoint	Treatment Effect (95% CI)
Average CS	−0.19 (−0.30, −0.09)
Average RMS	−0.20 (−0.34, −0.06)

Source: The reviewer created this table based on Tables 17 and 18 from the VO52.06 study report (p. 69-70).

Statistical Reviewer's Comment: *I have confirmed the secondary analyses in SAS 9.4 using the specified ANCOVA model. I calculated the percent difference from placebo using the least-squares means and variances from the ANCOVA model via the delta method assuming independence between the treatment and control means. These results, given in Table 5, are consistent with the results from the primary analysis.*

Table 5. Combined Intent-to-Treat Population Pollen Season Average Combined Score (CS) and Rescue Medication Score (RMS) Percent Differences from Placebo with 95% Confidence Intervals (CI)

Endpoint	% Difference from Placebo (95% CI)
Average CS	−26.3% (−41.6%, −10.9%)
Average RMS	−27.1% (−47.6%, −6.6%)

Source: The reviewer created this table using the VO52.06 dataset ef_dd.

6.1.2.4 Post-hoc Efficacy Analyses

A post-hoc repeated measures analysis of the daily CS, RTSS, and RMS during the pollen period was performed for the integrated summary of efficacy in the original BLA submission. A repeated measures ANCOVA, adjusted for pooled center, age, gender, asthma, grass sensitization status, and the number of days since the start of the pollen season was used to estimate the average treatment effect on the daily scores during the pollen season. The percent relative difference from placebo and 95% confidence interval were calculated by dividing the least-squares mean and 95% confidence interval for the treatment effect by the least-squares mean for the placebo.

Table 6. Daily Combined Score (CS), Rhinoconjunctivitis Total Symptom Score (RTSS), and Rescue Medication Score (RMS) Treatment Effect and Percent Relative Differences from Placebo with 95% Confidence Intervals (CI) for the Combined Intent-to-Treat Population

Endpoint	Treatment Effect (95% CI)	Relative Difference (95% CI)
Daily CS	−0.19 (−0.29, −0.08)	−30.1% (−46.9%, −13.2%)
Daily RTSS	−1.11 (−1.71, −0.51)	−30.6% (−47.0%, −14.1%)
Daily RMS	−0.19 (−0.33, −0.05)	−29.5% (−50.9%, −8.0%)

Source: STN 125471/0 Integrated Summary of Efficacy Tables 5.3.5.3.1-38 (p. 62), 5.3.5.3.1-39 (p. 65), and 5.3.5.3.1-40 (p. 68).

Statistical Reviewer's Comment: *There are several differences between these post-hoc models and the pre-specified models. The post-hoc analysis uses a repeated measures model that estimates the average difference between ORALAIR and placebo in the daily scores, while the pre-specified analysis estimates the difference between ORALAIR and placebo in the average score during the pollen season. The repeated measures model is adjusted for a linear trend in the outcome during the pollen season. Even if the models were similarly adjusted, the estimated treatment effects from these two models would not necessarily be the same. In the repeated measures model, subjects with multiple observations in the pollen period will contribute more information than subjects with fewer observations, while all subjects contribute equal information in the pre-specified model of the average outcome.*

I have confirmed the results for the treatment effect in the table above. While the daily CS treatment effect was estimated using restricted maximum likelihood (REML) with Kenwood-Roger degrees of freedom, the daily RTSS and RMS treatment effects were estimated using minimum variance quadratic unbiased estimation of the covariance parameters and the residual degrees of freedom. Preferably, these methods would not yield substantially different results. For the daily CS and RTSS, the two model fitting methods generally yield similar results. However, for the daily RMS model, the REML model fails to fit. This is probably because the RMS only takes values between 0 and 3 and many subjects have the same scores for the entire pollen season. This discreteness and lack of variability in the data can cause the model to fail to fit.

Regarding the results for the percent relative difference, the applicant calculated 95% confidence intervals using a method that does not account for the uncertainty in the estimate of the placebo treatment effect, yielding confidence intervals that are inaccurate. I have calculated the percent relative difference and confidence intervals using the delta method, which properly accounts for the variation in both the treatment effect estimate and the placebo effect estimate (Table 7). The slight differences in the point estimates for the percent relative differences are probably caused by differences in rounding when calculating the point estimates. The daily results are generally consistent with the results from the primary and secondary pre-specified analyses.

Table 7. Daily Combined Score (CS), Rhinoconjunctivitis Total Symptom Score (RTSS), and Rescue Medication Score (RMS) Percent Relative Differences from Placebo with 95% Confidence Intervals (CI) for the Combined Intent-to-Treat Population

Endpoint	% Difference from Placebo (95% CI)
Daily CS	−29.5% (−47.1%, −11.9%)
Daily RTSS	−30.4% (−47.9%, −12.8%)
Daily RMS	−28.5% (−51.2%, −5.9%)

Source: The reviewer created this table using the ef_dd dataset.

6.1.3 Efficacy Supplement Analysis & Results

In the clinical addendum from this efficacy supplement, the applicant presented the results of a post-hoc analysis of the VO52.06 efficacy data. A repeated measures ANCOVA of the daily CS in the ITT population, adjusted for pooled center, gender, asthma, grass sensitization status, age group, and treatment, was fit with an interaction term for treatment by age group.

This model yielded an estimated difference, comparing ORALAIR to placebo, in the average daily combined score of −0.19 (95% CI: −0.30, −0.08) with a non-significant interaction term for treatment effect by age group (p-value: 0.79).

Statistical Reviewer's Comment: *I have verified the applicant's results in SAS 9.4 using REML with Kenward-Roger degrees of freedom and asymptotic confidence intervals. The results are generally consistent with post-hoc analysis from the original BLA.*

The age groups used (5–11 and 12–17 years old) are not those of interest for this efficacy supplement. Furthermore, the hypothesis test of the interaction between treatment and age group compared the treatment effect in the 5–11 year old age group to the effect in the 12-17 year old age group. Because this hypothesis test failed to achieve statistical significance, no conclusion may be drawn. This comparison does not indicate whether the treatment effect in each group is consistent with the treatment effect in the combined data. The degree of similarity between the treatment effect in each age group and the treatment effect in the combined pediatric population depends on the relative sample size of each age group, the composition of each age group with respect to covariates, and the true effect size in each age group. Therefore, these results provide limited evidence of the efficacy in children aged 5–9 years old.

In an information request sent on March 23, 2018, the applicant was asked to conduct a post-hoc analysis of daily combined scores for children aged 5–9 and 10–17 separately, and in a second information request received on June 21, 2018, the applicant was asked to calculate the percent relative differences and 95% confidence intervals for the endpoints separately by age group. The results of this analysis, along with the results from the combined population, are shown in Table 8.

Table 8. Daily Combined Score (CS), Rhinoconjunctivitis Total Symptom Score (RTSS), and Rescue Medication Score (RMS) Treatment Effect and Relative Difference with 95% Confidence Intervals (CI) by Age Group

Endpoint	Age Group	Treatment Effect (95% CI)	Relative Difference (95% CI)
Daily CS	All	−0.19 (−0.29, −0.08)	−30.1% (−46.9%, −13.2%)
	5–9 years old	−0.26 (−0.45, −0.06)	−35.2% (−62.3%, −8.1%)
	10–17 years old	−0.14 (−0.27, −0.01)	−25.0% (−49.1%, −1.0%)
Daily RTSS	All	−1.11 (−1.71, −0.51)	−30.6% (−47.0%, −14.1%)
	5–9 years old	−1.64 (−2.67, −0.61)	−47.1% (−76.7%, −17.4%)
	10–17 years old	−0.87 (−1.78, 0.03)	−22.0% (−44.7%, 0.7%)
Daily RMS	All	−0.19 (−0.33, −0.05)	−29.5% (−50.9%, −8.0%)
	5–9 years old	−0.24 (−0.53, 0.05)	−27.3% (−60.2%, 5.6%)
	10–17 years old	−0.13 (−0.30, 0.04)	−29.3% (−66.5%, 7.9%)

Source: The reviewer created this table based on the Repeated Measures ANCOVA results from STN 125471/230.2 and the STN 125471/230.3 information request responses.

Statistical Reviewer's Comment: *These analyses use the same model as the post-hoc analyses from the original BLA submission, which is adjusted for the number of days since the start of the pollen season and has a random intercept for each subject. I have verified the results for the treatment effect and the point estimates for the percent relative difference but have not verified the 95% confidence intervals for the percent relative differences. As stated previously, the method the applicant used to calculate the confidence intervals for the percent relative differences did not properly account for the uncertainty in the estimate of the average daily score for the placebo group. I have calculated the 95% confidence intervals for the percent relative difference using the delta method, which properly accounts for this variability (Table 9). There are small differences in the point estimates for the relative differences because the applicant and I estimate slightly different treatment effect point estimates. The differences, which are on the order of 0.001, are not apparent in the rounded treatment effect results but are noticeable on the relative difference scale. These differences are likely caused by differences in numerical calculation or model fitting parameters.*

Table 9. Percent Relative Differences with 95% Confidence Intervals for Daily Combined Score (CS), Rhinoconjunctivitis Total Symptom Score (RTSS), and Rescue Medication Score (RMS) by Age Group

Endpoint	Age Group	Relative Difference (95% CI)
Daily CS	All	−29.5% (−47.1%, −11.9%)
	5–9 years old	−34.7% (−61.6%, −7.7%)
	10–17 years old	−24.4% (−51.6%, 2.9%)
Daily RTSS	All	−30.4% (−47.9%, −12.8%)
	5–9 years old	−47.1% (−75.3%, −19.0%)
	10–17 years old	−21.6% (−47.2%, 4.14%)
Daily RMS	All	−28.5% (−51.2%, −5.9%)
	5–9 years old	−26.5% (−60.2%, 7.1%)
	10–17 years old	−28.3% (−70.1%, 13.5%)

Source: The reviewer created this table using the VO52.06 ef_dd dataset.

The 95% confidence intervals for the age groups are wider than those for the combined population, as we would expect, because the age groups have smaller sample sizes. As we expect, the treatment effect for the combined population falls between the treatment effects for the two age groups. The results for daily RTSS for children aged 5–9 years old met the pre-specified success criteria of an upper 95% confidence interval less than −10%, but the results for daily CS and RMS did not. The results of this analysis suggest numerically similar or higher efficacy for children aged 5−9 years old compared to the other age subgroups. However, these post-hoc results are based on a small sample size and subjects were not randomized within these age subgroups. Therefore, these analyses may be underpowered and subject to residual confounding.

7. INTEGRATED OVERVIEW OF EFFICACY

Not applicable.

8. INTEGRATED OVERVIEW OF SAFETY

Not applicable.

9. ADDITIONAL STATISTICAL ISSUES

Not applicable.

10. CONCLUSIONS

In this supplement, Stallergenes S. A. submitted a reanalysis of the pediatric study VO52.06 from the original ORALAIR BLA. Study VO52.06 was a randomized, placebo-controlled, double-blind natural field study in subjects aged 5 to 17 years old in which subjects were treated 4 months before and throughout the pollen season. In this reanalysis, the applicant estimated the effect of two age groups (5–11 and 12–17 years old) on the treatment effect as measured by the daily Combined Score (CS), Rhinoconjunctivitis Total Symptom Score (RTSS), and Rescue Medication Score (RMS) using an ANCOVA model adjusted for pooled center, age group, gender, asthma, and grass sensitization status. This analysis found no statistically significant treatment by age interaction, suggesting that there is no evidence that the treatment effect is different between the two age groups. Therefore, no firm conclusions can be drawn from this analysis regarding difference in treatment effect between two age groups.

At CBER's request, the applicant completed a second post-hoc subgroup analysis by age group (5−9 years old vs. 10−17 years old) of the daily CS, RTSS, and RMS using a repeated measures ANCOVA model adjusted for pooled center, gender, asthma, grass

sensitization status, and the number of days since the start of the pollen season. For all three daily outcomes, the treatment effect in children aged 5–9 years old was greater than the treatment effect in children aged 10–17 years old and the treatment effect in both age subgroups was generally consistent with the combined pediatric results. The results for daily RTSS for children aged 5–9 years old met the pre-specified efficacy success criteria of an upper 95% confidence interval less than −10%, but the results for daily CS and RMS did not. The results of this analysis suggest numerically similar or higher efficacy for children aged 5−9 years old compared to the other age subgroups. However, these post-hoc results are based on a small sample size and subjects were not randomized within these age subgroups. Therefore, these analyses may be underpowered and subject to residual confounding.