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ORIGINAL RESEARCH ARTICLE

Economic Evaluation of 5-Grass Pollen Tablets Versus Placebo in the Treatment of Allergic Rhinitis in Adults

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Abstract
Background Allergen immunotherapy (AIT) is aimed at modifying the immune response to a causative allergen, thereby reducing clinical symptoms and symptomatic medication intake and improving quality of life. Long-term AIT research has led to the development of 5-grass pollen tablets, currently indicated for the treatment of grass pollen-induced allergic rhinitis (AR).
Methods A post-hoc analysis was conducted using the Average Adjusted Symptom Score (AAdSS) to compare the effect of treatment of AR with 5-grass pollen tablets versus placebo treatment. Using the results of the VO34.04 and VO53.06 trials and economic data, cost-effectiveness analysis of 5-grass pollen tablet treatment was performed from the Italian third-party payer perspective with cost data derived from a study of 2008 updated to 2011. Also a societal perspective was considered by using the costs related to the losses of productivity by following the human capital approach. Using the results of the analysis, the estimated receiver-operating characteristic curve was plotted to evaluate medication effectiveness in terms of quality-adjusted life years (QALYs) and a decision tree constructed to model the possible outcomes and costs for adults and paediatric patients with a low, medium, and high AAdSS. Finally, probabilistic sensitivity analysis was conducted to test the robustness of the results as well as their consistency at an assumed cost-effectiveness threshold of € 30,000/QALY.
Results The results indicate that compared to the placebo, the 5-grass pollen tablet treatment provides a benefit of 0.127 QALYs in medium AAdSS patients and of 0.143 QALYs in high AAdSS patients. The 5-grass pollen tablet treatment was found to cost € 1,024/QALY for patients with a medium AAdSS and € 1,035/QALY for patients with a high AAdSS. Of all the simulations performed in the probabilistic sensitivity analysis, 99 % indicated that the incremental cost-effectiveness ratio of the 5-grass pollen tablet treatment was below the threshold of € 30,000/QALY in patients with medium and high AAdSS, whereas it was found to be dominated in 67 % of simulations related to patients with low AAdSS.
Conclusion The 5-grass pollen tablet is a cost-effective treatment for adult AR patients with a medium or high AAdSS. This finding should be carefully considered when deciding the management strategy for these patients.

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1 Introduction

Allergic rhinitis (AR) is a significant health problem that the World Health Organization (WHO) estimates affects approximately 20 % of the world's adult population [1]. The severity of AR may vary considerably, depending on both individual and environmental factors. In severe cases,

treatment of AR requires a high consumption of pharmaceutical agents, such as antihistamines or corticosteroids, and can cause temporary inability to work or to carry out routine activities, leading to an overall temporary decline in quality of life (QoL). As indicated by the pharmacoeconomic literature on allergy to grass pollen, sublingual immunotherapy (SLIT) and subcutaneous immunotherapy (SCIT) have a more favourable cost-effectiveness profile than traditional treatments aimed only at treating the symptoms of allergy (rhinitis and asthma) in both adults and children [2–10]. Recent studies that have directly compared the costs of SCIT and SLIT have also indicated that treatment with the latter is more cost effective because of the cost reduction in terms of medical intervention needed for SCIT [9, 10].

In Italy, a multicentre study was conducted in 2006 to collect cost data for sublingual treatment with the grass pollen extract Staloral [11]. Comparison of these data with the data regarding the cost of traditional treatment provided to symptomatic patients showed that although the average annual cost of SLIT was greater (€ 311 vs. € 180), the use of SLIT led to a decrease in the amount expended on symptomatic drugs of between 22 % (in cases of rhinitis) and 34 % (in cases of rhinitis and asthma) [11]. As additional efficacy data [12, 13] indicate that treatment with the newly available 5-grass pollen tablets provides further clinical benefit, investigation of whether this benefit represents not only a clinical but also a pharmacoeconomic improvement would be very useful.

2 Methods

2.1 Structure of the Model

A decision model was developed to support the decision makers, with the aim of ensuring an optimum allocation of resources, and a discrete model was structured on the basis of a decision tree (Fig. 1) that reconstructs the main results of the VO34.04 and VO53.06 studies [12, 13]. The VO34.04 study took the Average Rhino-conjunctivitis Total Symptom Score (ARTSS) as the primary endpoint and the Average Rescue Medication Score (ARMS) as the secondary endpoint, and also considered the Average Adjusted Symptom Score (AAdSS), an endpoint based on the previous two endpoints. The VO53.06 study took the AAdSS as primary endpoint. The ARTSS corresponds to the average number of daily symptoms (from 1 to 6) experienced along a range of severity of 0–3, for a maximum total score of 18, whereas the ARMS attributes a score of 0–3 to a patient's AR symptoms according to the type of rescue medication used. The AAdSS weighs the clinical endpoint for the consumption of symptomatic drugs, thus permitting classification of the trial results according to whether a patient has a low, medium, or high AAdSS. By expressing the effectiveness of SLIT directly in relation with the cost reduction associated with the consumption of symptomatic drugs, the AAdSS is particularly useful for indicating the effectiveness of 5-grass pollen tablets in terms of this reduction. It was also possible to verify the improvement in QoL by using the threshold resulting from the receiver-operating characteristic (ROC) [14] curve estimated in the VO34.04 trial. The ROC curve returns a level of sensitivity and specificity for a test carried out on a dichotomic variable. The sensitivity and specificity indicators can be used to estimate the reliability of a null hypothesis in probabilistic terms as a discrimination threshold is varied. In the VO34.04 trial, the null hypothesis tested the AAdSS not to result in QoL improvement, and the discrimination threshold for a probability of 50 % was proven to be AAdSS = 1.45. In the decision model, the patients, all of whom presented with a low, medium, or high AAdSS in line with the distribution of cases presented in the VO34.04 trial, were assigned to either a 5-grass pollen tablet treatment group or a placebo treatment group. In each group, an improved or stable QoL corresponded to the treatment given to the group to which the patient was assigned. According to the results of the VO53.06 trial, this improvement occurred when the difference between the AAdSS scores in the 5-grass pollen tablet group before treatment and after treatment for 4 years, during which the patients were administered 5-grass pollen tablets for the first 3 years and simply followed up the remaining year, was more than 1.45 points.

2.2 Perspective

The model was populated with effectiveness and cost indicators, with the latter reflecting the Italian National Health Service (SSN—Servizio Sanitario Nazionale) perspective. To consider the results from a societal perspective in terms of the impact of AR on QoL and the performance of daily activities, including work tasks, productivity losses in terms of lost work days were evaluated using the human capital approach [15].

2.3 Effectiveness Estimate

The final endpoint was the difference in QoL with placebo, obtained from the 5-grass pollen tablet treatment in patients with a low, medium, or high AAdSS. The difference between the AAdSS for the 5-grass pollen tablets and the placebo (not administered with 5-grass pollen tablets but administered with symptomatic treatments) resulting from the VO34.04 and VO53.06 trials was converted in difference in QoL by

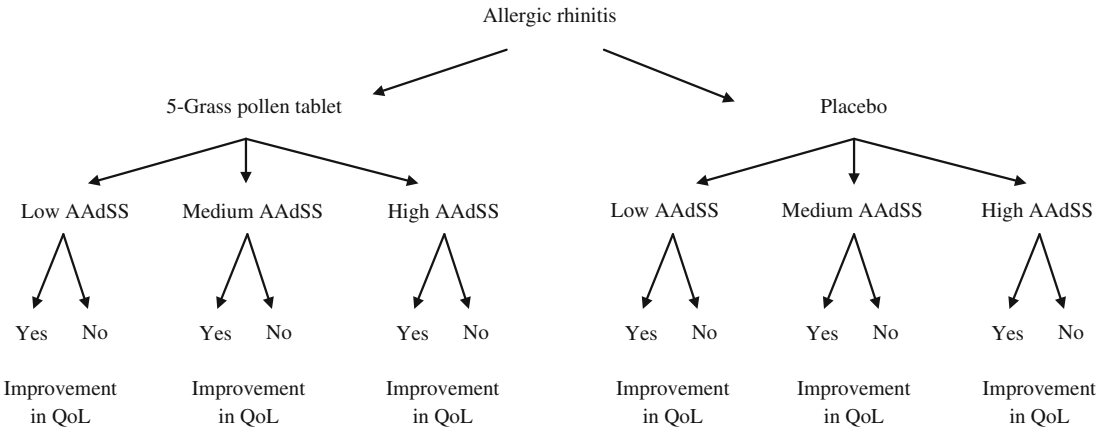

Fig. 1 Structure of the decision tree. *AAdSS* average adjusted symptom score, *QOL* quality of life

using the discrimination threshold of AAdSS = 1.45 resulting from the ROC curve, at which clinical improvement for adult patients may reflect an improvement in QoL in more than 50 % of cases. To derive the incremental QoL the following formula was used:

$$\Delta QoL = (AAdSS_{5gp} - AAdSS_{pl})/1.45$$

where ΔQoL is the the difference in quality of life, $AAdSS_{5gp}$ the AAdSS score of the 5-grass pollen tablet, and $AAdSS_{pl}$ the AAdSS score of placebo.

The ΔQoL indicator was used to adjust the 4-year time horizon of the model, thus obtaining incremental quality-adjusted life years (QALYs) produced by a 5-grass pollen tablet compared with placebo.

2.4 Cost Estimate

We used the results of the previous SIMAP study on Staloral [11], which was published in 2008, to estimate the cost parameters of AR in terms of allergy testing, spirometry, specialist medical examinations, intraocular drugs, corticosteroids drugs, and working days lost. These costs were assumed to be representative of the placebo groups of patients resulting from the VO34.04 and VO53.06 trials and were assigned prices and tariffs in accordance with the values reported in the outpatient specialist service list (year 2006), the Italian pharmaceutical formulary, and figures obtained from Italian National Institute of Statistics (ISTAT) employment market surveys in 2011 [16–18].

Therefore, we used the difference in the AAdSS between 5-grass pollen tablets and placebo resulting from VO34.04 and VO53.06 trials to estimate the percentage reduction of cost parameters related to the 5-grass pollen effectiveness. The difference in cost parameters resulting from the SIMAP study was estimated using the following formula:

$$\Delta COST^{a}_{SIMAP} = [(AAdSS_{5gp} - AAdSS_{pl})/(AAdSS_{pl})] \times COST^{a}_{SIMAP}$$

where $\Delta COST^{a}_{SIMAP}$ is the difference in cost "a" derived from SIMAP study, $AAdSS_{5gp}$ the AAdSS of the 5-grass pollen tablets, and $AAdSS_{pl}$ the AAdSS of the placebo group.

Finally, the 5-grass pollen tablet was priced at € 3 per tablet, under the assumption that the patients in the 5-grass pollen tablet treatment group would consume 150 tablets per year for 3 years. The expected treatment compliance rate of AR patients was assumed 70 % at baseline [19].

2.5 Discount Rate

The model covers a period of 4 years, which is consistent with prior studies conducted to evaluate the effectiveness of sublingual treatments, in which 3 years of administration were followed by a year of follow-up. The discount rate applied to the cost and effectiveness was 3 % per year.

2.6 Presentation of Results

The results are presented in the form of the incremental cost-effectiveness ratio (ICER), which considers the cost per ΔQoL obtained with 5-grass pollen tablet treatment in comparison with placebo treatment and is characterised by the AAdSS.

2.7 Sensitivity Analysis

In order to test the statistical consistency of the results, probabilistic sensitivity analysis was conducted [20]. On the basis of the clinical data obtained from the VO34.04 and VO53.06 studies, we considered the standard deviations, and we estimated the parameters (alpha and beta) of a gamma random distribution to simulate the variability of

the AAdSS and of the incremental costs. Other parameters whose variability was investigated were: compliance, discount rate, incremental QoL, and probability of the AAdSS to overcome the discrimination threshold (1.45) resulting from the ROC curve. The sensitivity analysis was conducted from the societal perspective.

3 Results

3.1 Effectiveness

Table 1 shows the effectiveness data included in the economic assessment. Table 2 shows the cost data and the changes following treatment with 5-grass pollen tablets compared to placebo treatment for patients with a low, medium, or high AAdSS. Figure 2 shows the ROC for adult patients, assuming a threshold value of 1.45 points. The sensitivity and specificity of the test for verifying the hypothesis reveal that the reliability coefficient of the adult QoL data is 0.825 [12]. On the basis of these data, an increase in QoL of 0.127 for a medium AAdSS and 0.143 for a high AAdSS were estimated for adult patients over a period of 4 years. No increase in QoL for patients with a low AAdSS was recorded.

3.2 Cost

Table 2 shows the additional costs (or savings) obtained by providing 5-grass pollen tablet treatment to AR patients in a manner that led to an increase in their AAdSS of least 1.45 points, the threshold value that corresponds to an improvement in QoL. These findings reflect the results of the SIMAP study [11], whose values were modified and updated to reflect outpatient service tariffs, and the costs indicated in the pharmaceutical formulary and ISTAT market surveys in 2011. For AR patients with a low AAdSS, incremental cost values are observed, as there was no improvement in their QoL, and as the increase in their AAdSS remained below the threshold, the 5-grass pollen tablet treatment represents a cost (in terms of the cost of the drug, diagnostic testing, etc.) that provides no significant benefits. From a NHS perspective and including patients with an AAdSS below the threshold for whom there is no improvement in QoL and considering all symptoms, the 5-grass pollen tablet treatment represents an increased cost of € 208 for patients with a low AAdSS, € 130 for patients with a medium AAdSS, and € 148 for patients with a high

Table 2 Annual incremental costs or savings in patients with an Average Adjusted Symptom Score (AAdSS) greater than 1.45 after 5-grass pollen tablet treatment

Cost parameter	Difference in cost compared to placebo (€)		
	Low AAdSS	Medium AAdSS	High AAdSS
Skin allergy testing	0.43	−27.87	−22.97
Test for IgE dosage	0.93	−60.97	−50.26
Spirometry	0.21	−13.93	−11.49
Medical examinations	0.19	−12.39	−10.21
Sublingual treatment with 5-grass pollen tablets	229.5	229.5	229.5
Antihistamines	0.07	−4.47	−3.69
Nasal sprays	0.20	−12.85	−10.59
Nasal obstruction	0.05	−3.12	−2.57
Intraocular antihistamines	0.09	−5.88	−4.85
Oral corticosteroids	0.01	−0.63	−0.52
Days off work	1.27	−83.04	−68.46

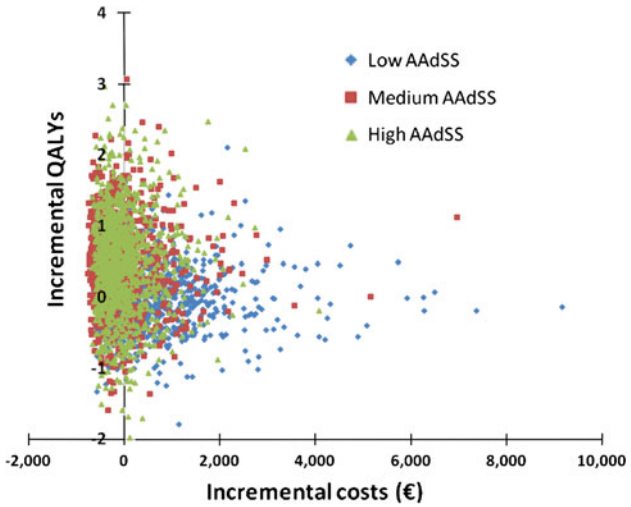

Fig. 2 Cost-effectiveness plane: incremental costs and QALYs produced by 5-grass pollen tablets. *AAdSS* average adjusted symptom score, *QALYs* quality-adjusted life years

Table 1 Effectiveness of treatment by Average Adjusted Symptom Score (AAdSS). Source: VO34.04 and VO53.06 studies [12, 13]

AAdSS category	5-Grass pollen tablets AAdSS score [mean (SD)]	Placebo AAdSS score [mean (SD)]	No. of subjects treated by 5-grass pollen tablet	No. of subjects treated by placebo	Incremental quality of life
Low	4.48 (3.19)	4.35 (2.56)	36	40	0
Medium	3.14 (2.63)	5.41 (3.97)	49	53	0.13
High	4.95 (3.93)	7.45 (3.91)	51	55	0.14

Table 3 Cost-effectiveness ratio of 5-grass pollen tablets versus placebo treatment by the Average Adjusted Symptom Score (AAdSS)

Perspective	Low AAdSS			Medium AAdSS			High AAdSS		
	Incr. costs	Incr. QALY	ICER	Incr. costs	Incr. QALY	ICER	Incr. costs	Incr. QALY	ICER
NHS	208	0	Dominated	130	0.127	1,024	148	0.143	1,035
Societal	232	0	Dominated	87	0.127	685	119	0.143	832

Incr. costs incremental costs, *Incr. QALY* incremental quality-adjusted life years, *ICER* incremental cost-effectiveness ratio, *NHS* national health system perspective

AAdSS. If productivity losses are also included in the analysis, the incremental costs decrease to € 87 for patients with a medium AAdSS and € 119 for patients with a high AAdSS but increase to € 232 for patients with a low AAdSS.

3.3 Cost-Effectiveness Ratio

Table 3 shows the results of the cost-effectiveness analysis of 5-grass pollen tablet treatment. Expressed in the form of the ICER, they indicate a value of € 1,024/QALY for patients with a medium AAdSS and € 1,035/QALY for patients with a high AAdSS from the NHS perspective. For patients with a low AAdSS, there is no gain in terms of QALYs, so the 5-grass pollen tablet treatment represents simply an extra cost of € 208, indicating that the cost-effectiveness ratio is dominated by the placebo. From a societal perspective, the ICER is € 685/QALY and € 832/QALY for patients with a medium and a high AAdSS, respectively, while the ICER continues to be dominated by the placebo for patients with a low AAdSS producing an extra cost of € 232.

3.4 Sensitivity Analysis

The sensitivity analysis evaluated the uncertainty of the cost parameters and QALYs included in the model and is characterised by the level of AAdSS. Results are summarised in Figs. 2 and 3. Figure 2 shows the cost-effectiveness plane, which simulates the incremental costs and QALY resulting from the variation of the compliance, AAdSS, and costs characterised by the level of AAdSS, whereas Fig. 3 categorises the results of the simulation according to the corresponding ICER and assigns a probability to each scenario corresponding to variations in cost parameters and costs. The results indicate that in 99 % of cases, the cost-effectiveness ratio is below € 30,000/QALY, which is the maximum willingness-to-pay threshold considered sustainable from empirical observation of past decisions of the leading international regulatory agencies. The medium and high AAdSS CEAC in Fig. 3 starts from 0.7 and 0.75, indicating that the cost-effectiveness ratio is dominant in 70–75 % of cases with a

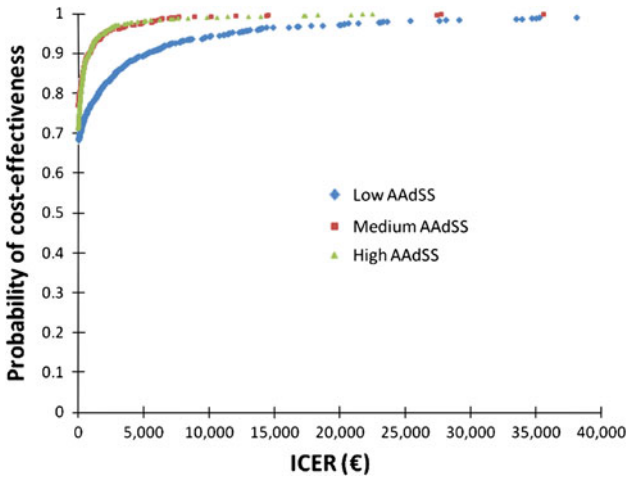

Fig. 3 Cost-effectiveness ratio acceptability curve (CEAC). *AAdSS* average adjusted symptom score, *ICER* incremental cost-effectiveness ratio

medium or high AAdSS, whereas the low AAdSS CEAC starts from 0.67, indicating no improvement in patients with a low AAdSS despite increased treatment costs. In only 33 % of cases with low AAdSS is the ICER below the threshold of € 30,000/QALY.

4 Discussion

This study estimated the cost-effectiveness ratio of the 5-grass pollen tablet treatment by comparison of the 5-grass pollen tablets treatment with placebo treatment based on a decision tree populated with hypothetical data. This assessment produced results that can be considered favourable from a sustainability point of view. The cost-effectiveness ratio acceptability curve based on the multivariate probabilistic sensitivity analysis shows that the cost-effectiveness ratio remains below the 'critical' threshold of € 30,000/QALY in nearly all scenarios simulated. This study has several strengths that contribute to the robustness of these findings. First, the effectiveness data that were used to constitute the structure of the model were taken from a double-blind randomised controlled trial [12, 13]. Second, the use of the AAdSS as an effectiveness indicator permitted identification of a direct relationship between the outcome and the

decrease in the consumption of resources (e.g. corticosteroids, diagnostic testing, etc.), which in part offsets the cost of 5-grass pollen tablets and thus makes a decisive contribution to the sustainability of NHS resources. Nevertheless, this study also faced several limitations. Although it used data derived from randomised controlled clinical trials, the model fits hypothetical scenarios. However, previous model-based studies of economic evaluation of AIT have provided significant findings in the understanding of the cost effectiveness of this treatment [10, 21]. Despite being estimated on the basis of the existence of a direct relationship between symptoms and the consumption of resources, the reliability of the cost-related part could be significantly improved if it were based on the resources actually consumed by patients using the microcosting method. Similarly, the utility coefficients, which were extrapolated using the ROC curve, could be measured directly by administering a questionnaire, such as the Euroqol (EQ 5D) [22], to AR patients. In fact, the EQ5D appears to be particularly appropriate for assessing AR, as severe or moderate AR may be presumed to have an impact on the patient's ability to perform everyday activities (e.g. sport, work, etc.) and his/her psychological condition. It is also true that the multivariate probabilistic sensitivity analysis conducted on the deterministic results of the study gives a sufficient safety margin as to the sustainability of the cost-effectiveness ratio, which would presumably remain below the threshold of € 30,000/QALY in any case, even if the model was populated with real data and different discount rates (varied between 1.5 and 5 % in the sensitivity analysis) were used. In particular, the discount rate potentially appears be one of the most sensitive parameters as the time horizon is limited to 4 years. In this sense, this study provides added value with respect to the previous economic assessments of the use of SLIT vaccines to treat AR [8–11]. Of note, the finding that the cost effectiveness of 5-grass pollen tablet treatment increases with the severity of AR symptoms agrees with the findings of a recent report regarding the higher clinical efficacy of the 5-grass pollen tablet treatment in patients with more severe AR [23]. In this analysis, the study centres were grouped into tertiles (low, middle, and high tertiles) according to the symptom severity scores observed in the placebo patients at each centre to assess the difference in the average score between the treatment and placebo groups in each tertile. The results indicated an increased treatment effect in the most severe patients, independent of the symptom score used, during pollen season. Of note, a recent study showed that the 5-grass pollen tablet is more cost-effective than the tablet containing only one grass, i.e. *Phleum pratense* [24]. This could be related to the fact that a 5-grass pollen preparation fits better with patient's sensitisation profile, as shown by laboratory studies [25] and botanical observations [26], and thus may result in higher clinical effectiveness.

Lastly, attention should be drawn to the need to examine the administration of SLIT from an organisational point of view. The results of the clinical trials [12, 13] used in the model show that the treatment is, in all cases, effective only when at a compliance rate of 75 % or greater. However, sensitivity analysis showed that increased levels of compliance result in an increase of the ICER which, anyway, remains under the € 30,000/QALY threshold even though a 100 % compliance is assumed. This percentage is clearly of fundamental importance for the NHS when considering the level of investment that will be remunerative in terms of health gains. Thus, awareness that treatment effectiveness depends on a high level of patient compliance and adherence, which could be achieved with adequate education both at the specialist allergy centres [27] and by general practitioners when providing SLIT, must be a primary consideration.

5 Conclusion

This analysis, performed using the optimal tools to estimate the cost effectiveness of a medical treatment, shows that the 5-grass pollen tablet is cost effective in adult patients with grass pollen-induced seasonal allergic rhinitis who have a medium or high average adjusted symptom score compared to standard drug treatment. This finding should be carefully considered when deciding the management strategy in patients with seasonal allergic rhinitis, who, in contrast, are generally treated by symptomatic drugs.

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Declaration of financial/other relationships Ilaria Dell'Albani, Franco Frati and Paola Puccinelli are employees of Stallergenes Italy. Cristina Romao is employee of Stallergenes SA. Cristoforo Incorvaia is a scientific consultant for Stallergenes Italy. The other authors have no conflicts of interest that are directly relevant to the content of the study.

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