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Oralair®: a causal treatment for grass pollen-induced allergic rhinoconjunctivitis

Grass pollen-induced allergic rhinoconjunctivitis is a common disease, comprising more than just the classic symptoms of nasal obstruction, sneezing, rhinorrhea and itchy, watery eyes. Sufferers deal with severe impairments in daily life. Allergic rhinoconjunctivitis is also considered an important risk factor in the development of asthma. Allergen avoidance, medication for symptomatic treatment and allergen-specific immunotherapy are cornerstones in therapeutic management, but immunotherapy is the only available treatment that is able to affect the natural course of allergy. In recent decades, clinical trials have investigated the efficacy and safety of subcutaneous immunotherapy. To date, efforts have been made to develop more convenient routes of administration. Substantial improvement may be achieved through the application of sublingual tablets. This article discusses the development process of immunotherapy and the clinical background of the Oralair® (Stallergènes, Hauts-de-Seine, France) five-grass pollen tablet. Furthermore, it outlines this tablet's efficacy and safety properties.

KEYWORDS: allergic rhinoconjunctivitis ■ five-grass pollen tablet ■ sublingual immunotherapy

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Allergic rhinoconjunctivitis is a major health issue, affecting more than 500 million people worldwide in their daily lives [1]. Two large surveys conducted in the USA in 2006 and 2007 revealed that 14% of the adult population and 13% of children suffer from allergic rhinitis [2,3]. In Europe, this disease has been found to be prevalent in 25% of the population with immense geographical variations [4,5]. The most frequent causes of sensitization are house dust mites and grass pollen. Many patients are polysensitized.

Although allergic rhinitis is not a direct cause of mortality, it escalates the risk of developing various secondary diseases such as asthma or comorbidities such as allergic conjunctivitis [1,6]. Thus, the economic impact of this chronic condition is substantial as a result of the high prevalence and the decrease in productivity during the allergy season. From 2000 to 2005, the costs of treating allergic rhinitis in the USA almost doubled from US\$6.1 to 11.2 billion [7].

Allergen avoidance, drugs and allergen-specific immunotherapy (SIT) are cornerstones in the management of rhinoconjunctivitis; however, immunotherapy is the only available treatment that is able to affect the natural course of allergy and that can possess disease-modifying effects. It offers an important opportunity for adequate symptom control, especially for allergic patients whose disease cannot be managed through symptomatic measures. Its success rate in pollen allergy sufferers is approximately 70–80% [8].

Since its first attempts in the early twentieth century, SIT was administered subcutaneously (SCIT) and was shown to be an effective treatment in children and adults. However, SCIT is a time-consuming procedure lasting up to 5 years and is burdened by the potential risk of severe adverse reactions. From 1990 to 2001, fatal reactions occurred at a rate of one per 2.5 million injections, with an average of 3.4 deaths per year in the USA [9]. This risk:benefit ratio problem has encouraged researchers to search for alternative administration routes. Sublingual immunotherapy (SLIT) appears to be better tolerated than SCIT, has an improved safety profile and is less time consuming because it permits administration outside of the doctor's office [10]. Sublingual allergen extract solutions, however, are not easy for patients to use since these drops have to be refrigerated and may therefore limit patients' compliance. Yet continuous use of SLIT during the treatment process is highly relevant for the effectiveness of treatment. Substantial improvement in patient compliance might be achieved by the use of sublingual tablets instead of drops. Currently, efficacy has been established in adults and children for two grass allergy immunotherapy tablets: Grazax®, manufactured by ALK-Abello in Hørsholm, Denmark, and Oralair®, by Stallergènes in Hauts-de-Seine, France.

This article provides further details on SLIT using Oralair in patients suffering from grass pollen-induced allergic rhinoconjunctivitis.

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Historical background to SLIT

Since its first attempts in the early 20th century, SIT was administered subcutaneously. Based on the idea of the vaccination, Noon aimed to achieve an effective method against ‘airborne toxins’ in 1911 [11]. Irrespective of this incorrect assumption of the mechanism, SIT was found to improve hay fever symptoms, resulting in an increased use of this treatment modality. The oral route of immunotherapy was suggested by Curtis in 1900 [12] and over the following years other routes of administration were proposed (FIGURE 1) [13]. The overall objective of all these efforts was to find a safer and more convenient route of administration.

The intensive investigation of the oral route of administration for respiratory disease started in 1970 when Morris first described using ultrasmall doses of antigens as SLIT [14]. In the following years, several trials investigated its efficacy and safety, but some had no allergen standardization, which resulted in marked variation in allergenic strength and controversial experiences using this therapy [15–18]. Oral administration was gradually abandoned during the following years [10].

After the British Committee for the Safety of Medicine raised concerns about the safety profile of SCIT as a consequence of reported deaths and in consideration of a growing market share of cheaper as well as effective drugs (e.g., oral H1 antihistamines), the interest in noninjection routes of immunotherapy increased again. Guidelines were installed, requiring manufacturers to produce only single-allergen preparations and were followed by those pertaining to the production of allergens and their standardization methods. Since the release of Guideline 2001/83/EC [101], allergens

have been defined as immunological medical products and require marketing authorization. In several countries, national regulations still allow marketing as ‘named patient preparations’.

The recommendation for the use of SLIT in children and adults with allergic rhinitis evolved over several years based on the following key publications: the WHO position paper on allergen immunotherapy [19]; the Allergic Rhinitis and its Impact on Asthma Workshop Group paper in collaboration with WHO [20] and its 2008 update [1]; the Cochrane review of SLIT for allergic rhinitis based on 22 studies involving 979 patients (children and adults) [21]; a meta-analysis evaluating the efficacy of SLIT in the treatment of allergic rhinitis in children and adolescents aged 3–18 years [22]; and the World Allergy Organization position paper on sublingual immunotherapy [10]. The optimal dose for the sublingual treatment of grass pollen-induced allergic rhinoconjunctivitis was identified [23] and a sustained effect of SLIT on symptoms after treatment cessation was shown [24]. Over the past 10 years, the allergen doses used for SLIT increased up to 1125-times the dose commonly administered with SCIT [25].

To date, SLIT has been tested in allergic rhinoconjunctivitis and asthma in more than 60 randomized, double-blind, placebo-controlled trials; approximately 24 studies have investigated the efficacy and safety of specific grass pollen immunotherapy, nearly nine trials of which concerned allergen tablets [26]. In general, the magnitude of efficacy varies greatly across studies and symptom improvement ranges from 10 to 45% in comparison with placebo [27]. Furthermore, with regards to safety, studies demonstrate that the SLIT regimen is superior to that of SCIT. No fatality has ever

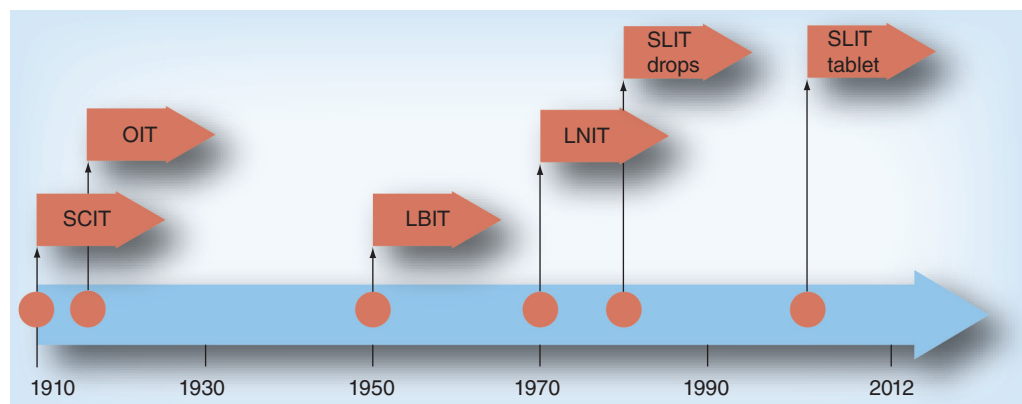


Figure 1. Historical development of application routes in immunotherapy.

LBIT: Local bronchial immunotherapy; LNIT: Local nasal immunotherapy; OIT: Oral immunotherapy; SCIT: Subcutaneous immunotherapy; SLIT: Sublingual immunotherapy.

been reported and cases of anaphylaxis are very rare (six in total) [28–32]. Larger trials in children also observed an absolute reduced risk of 36% for asthma occurrence after 3 years of follow-up. This means that only three children need to be treated to prevent one new onset of asthma [33].

In studies reported in 2010, allergen tablets Oralair and Grazax were tested in over 1605 subjects and showed a good safety profile [26]. Adverse events (AEs) are mainly local and resolved rapidly. In addition to significant improvements in symptom scores, studies also demonstrated a 20% improvement in quality of life in comparison with placebo [26]. Two pediatric trials included 531 randomized subjects and found significant differences between SLIT and placebo for symptom reduction and rescue medication. The frequency and profile of AEs was comparable to the adult studies [34,35].

Randomized controlled trials providing evidence for a direct efficacy comparison of SCIT and SLIT have not been published to date. A meta-analysis, which was conducted by Di Bona *et al.* and was based on trials that compared immunotherapy with placebo, provides indirect evidence [36]. The authors calculated a standardized mean difference (SMD) for the effect of immunotherapy on the symptom score. SLIT drops present a SMD of -0.23, SLIT tablets present a SMD of -0.40 and SCIT presents a SMD of -0.92. These results indicate that SCIT with grass allergens is more effective than SLIT in the control of symptoms. Comparable results were observed in the reduction of antiallergic medication. Di Bona *et al.* described a significant heterogeneity among the results of the included randomized controlled trials and stated the need for a comparative randomized trial to obtain clear evidence.

Chemistry, pharmacokinetics & metabolism

There are, to date, 13 groups of allergens, and two unrelated proteins – group one (glycoproteins) and five (nonglycosylated proteins) – have been identified as major allergens of grass pollen and account for more than 80% of the allergenic potential. Group two and three grass allergens have been identified as minor allergens and were found in 40–60% of sufferers [37,38].

Oralair tablets consist of a mixture of pollen from *Pooideae* grasses, which demonstrate significant IgE crossreactivity. Each tablet contains equal proportions of freeze-dried allergen extract from five kinds of grass pollen: perennial rye grass (*Lolium perenne*), meadow

grass (*Poa pratensis*), timothy grass (*Phleum pratense*), cocksfoot/orchard (*Dactylis glomerata*) and sweet vernal (*Anthoxanthum odoratum*) at a dose of 100 or 300 indexes of reactivity (IR). The dosage of 300 IR corresponds to approximately 20–25 µg/ml of the group of five major allergens [23,35]. The aim of Oralair is to induce an immune response to the allergen and to modify the cascade of underlying adverse immune responses in an antigen-specific manner.

Clinical efficacy, use of rescue medication & quality of life

Oralair is used for the treatment of patients with grass pollen-induced allergic rhinitis with or without conjunctivitis.

Several randomized, placebo-controlled trials in children and adults have demonstrated symptom reduction, as well as rescue medication reduction in, comparison with placebo. SUPPLEMENTARY TABLE 1 (see online at www.futuremedicine.com/doi/suppl/IMT.12.147) gives an overview of the study designs used within the relevant trials investigating the five-grass pollen tablet.

■ Allergen challenge chamber

Clinical trials within the field of allergy in particular have to deal with a lack of standardized exposure and natural year-to-year variations in the onset and peaks of the pollen season. Furthermore, patients' degrees of exposure are influenced by individual daily routines and avoidance strategies. Consequently, these factors could bias study results. Investigations using an allergen challenge chamber (ACC), also known as an environmental exposure unit, make it possible to assess the efficacy of an intervention under controlled conditions. They allow identical repeated exposure and assessment of changes in a patient's response over time.

A randomized, placebo-controlled trial conducted by Horak *et al.* between 2007 and 2008 assessed the efficacy and onset of action of the five-grass pollen tablet in 89 adults suffering from moderate-to-severe grass pollen-induced rhinoconjunctivitis in an ACC [39]. After screening and a 2-h allergen challenge at baseline, patients were randomized to receive either a 300 IR tablet or placebo. Additional challenges were performed after 1 week and then after 1, 2 and 4 months of treatment. Each follow-up challenge lasted at least 4 h. Before (baseline) and during exposure, patients used a score ranging from 0 (no symptoms) to 3 (severe symptoms) to rate their rhinitis and conjunctivitis symptoms:

sneezing, rhinorrhea, nasal and ocular pruritus, nasal congestion and tearing. Furthermore, nasal airflow and nasal secretion weight were measured within predefined time slots. For the 300 IR group, the intention-to-treat analysis demonstrated a significantly lower average total symptom score during pollen challenge after 4 months of treatment than for the placebo group (4.85 ± 1.967 vs 6.87 ± 3.114), representing a relative mean improvement of 29.3%. Mean changes in nasal airflow and nasal secretion weight did not achieve statistical significance in comparison to placebo after 4 months of treatment. A per-protocol analysis confirmed these results.

■ Phase II & III trials

In Europe, a large, multinational, randomized, double-blind, placebo-controlled study was performed by Didier *et al.* with the purpose of determining the optimal effective and safe dose of tablet-based SLIT in 2005 [23,40–42]. A total of 628 adult patients from 42 centers in ten European countries were included, randomized and given one of three daily doses (100, 300 or 500 IR) or placebo. Each patient group received their first dose under the investigator's supervision 4 months before the expected start of the grass pollen season. The first 5 days of therapy were used as a titration phase until the final dose was achieved (SUPPLEMENTARY TABLE 1). In total, the following visits were scheduled per patient: at screening; randomization; 2 weeks after randomization; 4 weeks before the estimated start of pollen season; at season's peak; at the end of the pollen season; and at a 2-week follow-up visit.

For the intention-to-treat population, investigators observed a dose–response effect; the 100-IR dose was more effective than placebo but less effective than the 300- and 500-IR doses. In comparison with patients under placebo, sufferers receiving 300 IR demonstrated an improvement of 37% and reported significantly less rescue medication use (46%). Patients receiving 500 IR experienced 35% symptom reduction. These improvements have to be characterized as clinically meaningful. The results also indicate that the plateau of efficacy was reached under a dosage of 300 IR because 500 IR did not increase the efficacy in a clinically significant manner [23]. The 300-IR dose therefore seems to be the optimal allergen dose for SLIT. The analysis of the per-protocol group yielded similar evidence. In addition to the symptom scores, quality of life, assessed using the Rhinoconjunctivitis Quality

of Life Questionnaire, improved significantly ($p < 0.01$) within the active treatment groups. In terms of the impact on ocular symptoms, the study outcomes for watery and itchy eyes revealed a significant reduction in these impairments when comparing the 300- and the 500-IR tablet dose with placebo.

A multicenter, randomized, controlled trial conducted by Didier *et al.* from 2007 to 2011 highlighted the long-term effect of pre- and co-seasonal administration of the five-grass pollen tablet [43]. Patients received either placebo or one 300-IR five-grass pollen tablet sublingually once daily for 2 or 4 months before the pollen season and then coseasonally for three consecutive pollen seasons (2007, 2008 and 2009). The years 2010 and 2011 were used as follow-up. In total, 633 patients were randomized into the study; after the third study year, 465 patients had finished the treatment period. After three seasons of treatment, the average daily adjusted symptom score was reduced in comparison to placebo by 34.8% for patients who started treatment 4 months before the pollen season and 37.7% for participants who received therapy 2 months prior to the season. Therefore, a shorter pretreatment phase might be sufficient and consequently more cost-effective. Furthermore, the Rhinoconjunctivitis Quality of Life Questionnaire showed significant changes for the 4- and 2-month groups versus placebo.

The efficacy and safety of five-grass pollen tablets have also been examined in pediatric patients. Allergic rhinoconjunctivitis is the most common chronic allergic disorder affecting children and constitutes a significant burden for patients and their families. Poorly controlled symptoms may cause sleep impairment and learning problems. Besides these obvious health problems, children suffering from allergic rhinitis have a higher risk of new-onset asthma. Since SIT is the only treatment that can prevent the development of asthma, SCIT is also frequently used in children, although it is associated with inconvenient injections and the risk of serious AEs. SLIT formulations, especially tablets, seem to be more safe and acceptable, which leads to an improved effectiveness of immunotherapy. In a multicenter, multinational, double-blind, placebo-controlled study in children with grass pollen-induced allergic rhinoconjunctivitis, Wahn and colleagues determined whether the 300-IR dose of the five-grass pollen tablet was effective and safe [35,44]. The authors chose a pre/co-seasonal regimen starting 4 months before the expected start of the pollen season

and continuing throughout the season. The study was conducted between December 2006 and September 2007, and included 278 children between 5 and 17 years of age. Patients were screened and randomized to receive either the 300-IR tablet or placebo. Similar to the adult study by Didier *et al.* [23,40–42], Wahn and colleagues used a titration phase [35,44]. The SLIT dose was increased by 100 IR per day over 3 days. The placebo group received the same number of tablets. The primary outcome was the efficacy of treatment on the rhinoconjunctivitis total symptom score. Impairments were rated from 0 (no symptoms) to 3 (severe symptoms). In addition, participants and their parents had to complete a daily diary. Further outcome measures were usage of rescue medication and a production of allergen-specific blocking IgG4 antibodies and an increase of grass pollen-specific IgE. During the pollen season, the primary efficacy results demonstrated a significantly lower mean rhinoconjunctivitis total symptom score in the 300-IR group in comparison with placebo. The active group showed a 28.0% greater mean improvement than the placebo group. Data for the per-protocol analysis were similar. Furthermore, the mean rescue medication score of the 300-IR group was markedly different from that of the placebo group. Patients receiving the active substance had 24.1% lower usage of rescue medication. TABLE 1 summarizes all of the studies discussed above.

Safety & tolerability

The allergen tablet is generally well tolerated and shows an acceptable safety profile in children and adults.

Trials examining the safety and tolerability of tablets display two types of events in their safety statistics:

- AEs: any medical problem experienced by a study participant that is not a benefit to the individual whether or not it is considered intervention related;
- Treatment-emergent AEs (TEAEs): any event not present prior to the initiation of the treatment or any event already present that worsens in either intensity or frequency following exposure to the treatment.

■ Adverse events

The safety and tolerability of different doses of grass pollen tablets in SLIT were examined by Larsen *et al.* in a randomized, double-blind,

placebo-controlled Phase I study [45]. The authors observed 30 adults aged 18–50 years who were allergic to grass pollen over ten treatment days. Patients received either 100, 200, 300, 400 or 500 IR, or placebo. A total of 91 AEs were reported during treatment; 85 occurred in the SLIT groups and six in the placebo group. AEs occurred mainly locally; all were assessed as mild to moderate and resolved rapidly without intervention. No serious AEs were reported. Furthermore, these data demonstrate that short-term build-up may be more tolerable than immediate start with maintenance dose.

The randomized controlled trial by Horak *et al.* investigating the safety of Oralair under controlled conditions in an ACC observed a total of 73 TEAEs in both groups [39]. A total of 60% of the active group patients and 31.8% of patients in the placebo group reported these events. All TEAEs in the 300 IR group were mild and there were no serious AEs. The most frequent events (35.6%) were oral pruritus and throat irritation.

In the clinical trial conducted by Didier and colleagues [23,40–42], a total of 384 patients reported TEAEs. Compared with placebo (48.7%), patients receiving active treatment experienced TEAEs more often (68.8% 100 IR; 62.6% 300 IR; 64.4% 500 IR). Most AEs were mild or moderate, and varied greatly in duration. The AE with the highest incidence in all subgroups was oral pruritus. Between 1.9 and 6.4% of patients reported severe AEs, usually oral pruritus or, more rarely, gastrointestinal pain.

Oralair also appears to be safe for long-term use. A randomized controlled trial conducted by Didier *et al.* demonstrated a good safety profile over 3 years and showed that the tolerability of the 300-IR five-grass pollen tablets improved during the study period [43]. The incidence and severity of TEAEs decreased each year from 80% at the beginning to 54% after 3 years.

For children, the safety was investigated in a separate multicenter, multinational, double-blind, placebo-controlled clinical trial [35,44]. Five patients reported serious AEs – two in the active and three in the placebo group – but no event was attributed to the study treatment. In all, 902 TEAEs were documented in 232 patients (84.9% in the 300-IR group and 82% in the placebo group). The majority of TEAEs were mild to moderate. Similar to the adult study, oral pruritus was the AE with the highest incidence. Therefore, the rate and severity of side effects observed for children in this clinical trial were similar to those reported in other tablet-based SLIT studies (TABLE 1).

Table 1. Summary of study results for the five-grass pollen tablet.

Study (year)	Study population (n)	ITT	Main treatment duration	Efficacy	Safety	Ref.
Adults						
Larsen <i>et al.</i> (2006)	30	28	10 days	–	Group 1 and 2 (n = 12: 100, 200, 300, 400 and 500 IR; n = 4: plc): 55 AEs – mild-to-moderate intensity Group 3 (n = 6: 300 IR; n = 1: plc): 16 AEs – mild-to-moderate intensity Group 4 (n = 5: 500 IR; n = 2: plc): 14 AEs – mild-to-severe intensity	[45]
Didier <i>et al.</i> (2007); Malling <i>et al.</i> (2009)	628	569	6 months	Rhinoconjunctivitis symptoms: 37% symptom reduction for the 300-IR group vs plc 35% symptom improvement for the 500-IR group vs plc Median proportion of symptom-free days: 300-IR group: 15.65% 500-IR group: 11.11% 100-IR group: 3.33% Plc group: 2.93% Days with rescue medication: 46% reduction of rescue medication for the 300-IR group vs plc	Frequency of AEs: Plc: 48.7% 100-IR group: 68.8% 300-IR group: 62.6% 500-IR group: 64.4% AEs: Oral pruritus 5.1% plc, 19.7% 100 IR, 25.8% 300 IR, 25.6% 500 IR Headache 13.5% plc, 14.6% 100 IR, 14.2% 300 IR, 8.8% 500 IR Throat irritation 3.2% plc, 11.5% 100 IR, 9.0% 300 IR, 14.4% 500 IR Nasopharyngitis 7.1% plc, 10.2% 100 IR, 8.4% 300 IR, 7.5% 500 IR Mouth edema 0% plc, 3.2% 100 IR, 4.5% 300 IR, 6.3% 500 IR Ear pruritus 0.6% plc, 5.1% 100 IR, 3.2% 300 IR, 4.4% 500 IR Tongue edema 0% plc, 3.2% 100 IR, 2.6% 300 IR, 5.6% 500 IR Pruritus 0.6% plc, 6.4% 100 IR, 1.9% 300 IR, 1.9% 500 IR	[23,42]
Horak <i>et al.</i> (2009) (ACC)	89	82	4 months	Average rhinoconjunctivitis symptoms: 29.3% symptom improvement vs plc after 4 months	Frequency of treatment-emergent AEs: plc: 31.8% 300 IR: 60.0% Treatment-emergent AEs: Oral pruritus 0% plc, 35.6% 300 IR Headache 18.2% plc, 17.8% 300 IR Throat irritation 0% plc, 35.6% 300 IR Nasopharyngitis 9.1% plc, 4.4% 300 IR Ear pruritus 0% plc, 6.7% 300 IR	[39]

ACC: Allergen challenge chamber; AE: Adverse event; IR: Index of reactivity; ITT: Intention to treat; plc: Placebo.

Table 1. Summary of study results for the five-grass pollen tablet (cont.).

Study (year)	Study population (n)	ITT	Main treatment duration	Efficacy	Safety	Ref.
Adults (cont.)						
Didier <i>et al.</i> (2009)	633	581 (1 year) 465 (3 years)	4–6 months per year; in total, 3 years	Average daily adjusted symptom score: 34.8% symptom reduction for the 4-month preseason group vs plc after 3 years 37.7% symptom improvement for the 2-month preseason group vs plc after 3 years Symptom- and medication-free days: 37.9% of days for the 4-month preseason group in season three 36.9% of days for the 2-month preseason group in season three 26.4% of days for plc in season three	Frequency of treatment-emergent AEs: Active and plc Year 1: 80% of patients Year 2: 62% of patients Year 3: 54% of patients Incidence of local reactions in patients receiving active treatment: Year 1: >57% Year 2: >43% Year 3: >36%	[40]
Children & adolescents						
Wahn <i>et al.</i> (2009); Halken <i>et al.</i> (2010)	278	266	6 months	Average rhinoconjunctivitis symptoms: 27.9% improvement for the active group (300 IR) vs plc at peak of pollen season 28% reduction for the active group (300 IR) vs plc during whole pollen season Symptom-free days: 22.6% of days for the active group 12.7% of days for plc Proportion of days with at least one rescue medication: During pollen season: 35.4% of days for the active group 46.5% of days for plc At pollen peak: 42.9% of days for the active group 56.3% of days for plc	Incidence of treatment-emergent AEs: Children (5–11 years of age) Active group: 86.2% plc: 82.4% Adolescents (12–17 years of age) Active group: 82.7% plc: 81.5% Patients with: Oral pruritus 4.3% plc, 33.1% 300 IR Cough 26.6% plc, 25.2% 300 IR Nasopharyngitis 12.9% plc, 13.7% 300 IR Mouth edema 0% plc, 12.9% 300 IR	[35,44]

ACC: Allergen challenge chamber; AE: Adverse event; IR: Index of reactivity; ITT: Intention to treat; plc: Placebo.

■ Pregnancy & lactation

Currently, no clinical data are available for Oralair use during pregnancy. If pregnancy occurs during treatment, therapy may be continued under strict supervision. Also, no data are available for therapy during lactation.

Regulatory affairs

Oralair was first authorized for commercial use in Germany in June 2008 and received marketing authorization across Europe in November 2009.

Conclusion & future perspective

To date, studies have shown that five-grass pollen SLIT tablets are well tolerated and effective in reducing the symptoms of rhinitis and conjunctivitis caused by grass pollen in

adult and pediatric populations. The 300-IR dosage appears to be optimal for both adult and child populations. Clinical trials described in the literature have demonstrated first-season efficacy of SLIT tablets given pre- as well as co-seasonally. In addition, long-term data were able to demonstrate the efficacy and safety of 300-IR tablets for grass pollen-induced allergic rhinoconjunctivitis over three seasons of therapy and to show a reduction in symptomatic medication use.

Nevertheless, additional long-term immunotherapy studies would be useful in establishing the optimal duration of treatment regimens.

Future fields of application will be developed for other pollen-induced diseases such as allergic asthma.

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Executive summary

Historical background to sublingual immunotherapy

- Immunotherapy is the only available treatment that is able to affect the natural course of allergy. It can have a disease-modifying effect and may thereby prevent secondary diseases of allergic rhinitis.
- Several well-designed clinical trials have investigated the efficacy and safety of immunotherapy. In recent decades, many efforts have been made to develop convenient routes of administration. The sublingual tablet form appears to be a promising possibility.
- Recently, five-grass pollen tablets for the treatment of grass pollen-induced allergic rhinoconjunctivitis have been developed.

Clinical efficacy, use of rescue medication, quality of life & safety

- Multinational, randomized clinical studies show an appropriate safety profile for these tablets. Furthermore, the trials offer strong evidence for the efficacy of the five-grass pollen tablets in comparison with placebo.
- A Phase III study investigated long-term treatment with Oralair® (Stallergènes, Hauts-de-Seine, France) over a period of three consecutive pollen seasons and a total observation time of 5 years. The results of this trial demonstrate a sustained treatment effect and a decreasing time trend for the incidence of treatment-emergent adverse events.

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