

EXPERT
REVIEWS

Five-grass-pollen sublingual immunotherapy tablet for the treatment of grass-pollen-induced allergic rhinoconjunctivitis: 5 years of experience

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Oralair® (OA) (Stallergenes, Antony, France) is a unique pre- and co-seasonal 5-grass-pollen sublingual immunotherapy tablet launched in 2008, and now approved in 31 countries worldwide for the treatment of grass-pollen allergic rhinitis and rhinoconjunctivitis. OA is the first oral treatment with a consistent, well-balanced allergen extract that mimics natural exposure and sensitization. A wealth of data exists from over 5 years of clinical and real-world experience demonstrating the efficacy and safety of OA for grass-pollen-allergy treatment. OA is highly effective from the first pollen season in all patient subgroups, including children and those with comorbid mild asthma, irrespective of sensitization status and symptom severity. OA also has sustained long-term benefits for symptom control and quality of life. This article provides an overview of the pharmacodynamics and pharmacology of OA; its efficacy, safety, tolerability and cost-effectiveness for the treatment of allergic rhinitis and rhinoconjunctivitis and its role in clinical practice.

KEYWORDS: 5-grass-pollen tablet • allergic rhinitis • allergic rhinoconjunctivitis • allergen-specific immunotherapy • clinical trial • efficacy • pollinosis • safety • sublingual immunotherapy

Allergic rhinitis (AR) is a common chronic inflammatory illness, characterized by rhinorrhea, nasal congestion, sneezing, nasal and ocular pruritis and watery eyes [1]. Inhalation of allergens by sensitized individuals triggers the IgE-mediated release of inflammatory mediators and cytokines, leading to a rapid appearance of symptoms [2]. AR has historically been classified as 'seasonal' or 'perennial' depending on whether symptoms occur with seasonal exposure to aeroallergens or are present throughout the year. Seasonal AR is most commonly attributed to plant pollen and other outdoor allergens, while perennial AR is associated with indoor allergens, such as dust mites, mold, cockroaches and pet dander, although it can also be associated with pollen in areas where this is prevalent year-round [3,4].

In 2001, the WHO-sponsored Allergic Rhinitis and its Impact on Asthma meeting produced guidelines proposing an alternative classification of the condition into 'intermittent' or 'persistent' AR, and grading symptoms as 'mild' or 'moderate/severe' [5]. Globally, the prevalence of seasonal ('hay fever') and perennial AR ranges from 7 to 42 and 1 to 13%, respectively, with the former being more common in children than adults [6]. The length of exposure to seasonal allergens is dependent on geographic location and climatic conditions [4]; in Europe, the main pollen season typically occurs from March to July, with slight variations according to latitude [7].

Approximately 500 million people worldwide [6], including an estimated 30–60 million in the USA [4] and 113 million in Europe [8],

suffer from AR, and its prevalence is increasing in most countries [2]. It is estimated that from 10 to 30% of adults and up to 40% of the pediatric population have AR [3,9]. While AR does not directly lead to mortality, it places a considerable burden on affected individuals, who often have a reduced quality of life (QoL), compared with non-sufferers [10]. The physical symptoms of AR can cause sleep disturbances, leading to daytime fatigue and somnolence, decreased cognitive functioning, absenteeism from school and work and impaired performance at school and work [11]. AR may also affect mood and social functioning [11] and can even contribute to sexual dysfunction in adults [12].

Moreover, in children, AR is often comorbid with chronic middle-ear effusions, sinusitis, adenoidal and tonsillar hypertrophy and acute and serious otitis media [9]. The co-existence of allergic conjunctivitis in patients with AR is widely recognized [13,14]. In a recent study, allergic conjunctivitis was identified in 53.5% of patients with AR, a finding comparable to those from other studies [15]. More than one-third of patients with AR have asthma [2]; AR frequently precedes the development of asthma and has been proposed as an independent risk factor for it [16].

Both US and EU guidance recommend that management of AR combines patient education with specific allergen avoidance, symptomatic pharmacotherapy and allergen-specific immunotherapy (AIT) [1,2,4]. It is typically not possible to eliminate exposure to pollen; therefore, drug treatment is often necessary to provide symptomatic relief. Medications for the treatment of AR and allergic rhinoconjunctivitis (ARC) include oral and intranasal second-generation H₁-antihistamines, intranasal glucocorticosteroids, leukotriene-receptor antagonists, oral and topical decongestants and intranasal anticholinergic agents [2,4], as well as combinations of these drugs. They are generally well tolerated and effective at alleviating those ocular and nasal symptoms mediated by histamine, such as rhinorrhea, itching and sneezing, but have only modest effects on nasal congestion [2]. To treat nasal blockage, oral decongestants may be used in adults with AR, as monotherapy or in combination with oral H₁-antihistamines, but systemic side effects are common [2,4]. Intranasal glucocorticosteroids are the most effective medication class for managing AR in adults and children, and have excellent tolerability [2,4]. However, treatment success for nasal therapies can be affected by poor patient adherence and administration technique [17]. Moreover, despite the use of optimal pharmacotherapy, patients with AR and ARC often fail to achieve complete alleviation of their symptoms or long-term control. Medications help to reduce the incidence and severity of symptoms, but are unable to modify the course of disease and are not curative [2].

In contrast, AIT is the only disease-modifying intervention available for the treatment of AR/ARC and involves repeatedly exposing the immune system of ARC patients to small amounts of the disease-causing allergen, inducing immunotolerance and ameliorating symptoms [18]. As such, US and EU guidelines recommend to consider AIT for patients with AR

who have demonstrable evidence of allergen involvement in their symptomatology [2,4]. AIT also appears to prevent the development of new allergen sensitizations and reduce the risk of subsequent asthma in patients with AR [19]. Its benefits may persist for several years following cessation of treatment [20]. The preventive benefits of AIT may be greater if initiated early in the course of the allergic disease [21,22]. AIT administered subcutaneously (subcutaneous immunotherapy [SCIT]) has demonstrated efficacy at reducing the symptoms of AR caused by plant pollens, and the use of symptomatic pharmacotherapy in patients with AR and ARC [23,24]. However, the necessity for multiple injections over a period of years, and the possibility of serious systemic side effects or life-threatening anaphylaxis, especially in patients with comorbid asthma [25], has prompted the development of alternative routes of administration.

Sublingual immunotherapy (SLIT), involving local absorption of allergens under the tongue, is easy to administer at home and does not require injections. SLIT is effective at ameliorating the symptoms of AR and ARC and appears to have a better safety profile than SCIT [21,26]. In an indirect comparison, grass-pollen SLIT tablets had a greater mean relative clinical impact than second-generation H₁-antihistamines and montelukast, and the same mean relative clinical impact as nasal corticosteroids [27]. Moreover, SLIT with a 5-grass-pollen allergen tablet for three consecutive pollen seasons has been shown to provide a sustained benefit in terms of symptom control and QoL, for at least 2 years after discontinuation of treatment [28–30], thus demonstrating long-term disease remission and modification that is consistent with the induction of antigen-specific tolerance [21].

Studies on SLIT adherence (generally defined as taking ≥80% of prescribed medication) have reported rates of between 29 and 91% over 2 or 3 years of treatment [31]. Factors that have been shown to be important for adherence to AIT include cost; inconvenience; feelings of inefficacy; adverse events (AEs); patient, parent and physician education and number of follow-up visits [21,32]. Lack of adherence to SLIT may also be caused by the incorrect perception that upon improvement in allergic symptoms, there is no further need to continue therapy [19].

AEs with SLIT are generally minor and local (such as oral irritation or ear pruritus), resolving spontaneously, and anaphylaxis is extremely rare (one study reported 11 non-fatal cases from an estimated 1 billion SLIT doses administered since 2000 [26]), as are serious systemic side effects (a comprehensive review of 104 publications on SLIT found 169 of 314,959 administered doses [0.056%] were classified as producing systemic reactions) [21,33,34]. According to recent guidance from the World Allergy Organization, SLIT may be considered as first-line therapy for AR and ARC, and failure of prior pharmacological treatment is not a requirement for its use [21]. The favorable safety profile of SLIT, and its regimen that does not require needles or frequent trips to a medical clinic, may make it more accessible to children and their caregivers and allow for treatment initiation at an age where disease progression may be more readily interrupted [21].

This review will focus on the 5-grass-pollen allergen tablet for the treatment of AR and ARC, and discuss its notable features and characteristics; pharmacology; the most recent data on its clinical efficacy, safety and tolerability and its role in clinical practice.

Overview of available sublingual immunotherapies for grass-pollen allergy

As previously noted, SLIT has many advantages over SCIT in terms of tolerability/safety and convenience. The most promising SLIT delivery systems are tablets and aqueous or glycerinated liquid allergen extracts ('SLIT drops'), both of which have been approved in Europe and several other countries for the treatment of ARC in adults and children aged >5 years [26,35]. The former approach consists of a rapidly dissolving tablet that is placed under the tongue, while the latter is an aqueous allergen extract administered as drops, which is held under the tongue for a few minutes and then swallowed (although some clinical trials have also evaluated spitting out of residual liquid, instead of swallowing) [35].

Until only recently, SCIT was the sole on-label option for AIT management of grass-pollen allergy in the USA, although some physicians use subcutaneous aqueous allergen preparations off-label for sublingual desensitization in allergic patients [33]. In April 2014, Oralair® (OA) (Stallergenes, Antony, France) became the first SLIT to be licensed in the USA for the treatment of grass-pollen-induced AR with or without conjunctivitis. OA was already the first grass-pollen-allergy SLIT tablet licensed in North America, having been granted marketing approval in Canada in 2012.

Introduction to 300 index of reactivity 5-grass-pollen tablet

OA is a 300 index of reactivity (IR) (a measure of biological potency [skin reactivity]) used to describe the strength of an allergen extract. The allergen extract contains 100 IR/ml when, on a skin prick-test using a Stallerpoint®, it induces a wheal diameter of 7 mm in 30 patients sensitized to this allergen (geometric mean). Five-grass-pollen SLIT tablet has been approved as immunotherapy for the treatment of confirmed grass-pollen-induced AR with or without conjunctivitis in more than 30 countries worldwide, including the USA, Canada, most European countries, Russia, Turkey and Australia. The approved indications and prescribing information for the SLIT tablets vary slightly between countries, and local prescribing information should be consulted for specific details [29]. OA is the first oral treatment with a consistent and well-balanced 5-grass-pollen allergen extract that mimics natural exposure and sensitization [36].

The first OA dose should be administered under the supervision of a physician with experience in the diagnosis and treatment of severe allergic reactions, and patients should be monitored for at least 30 min for any signs of this occurring [29]. If the first dose is well tolerated, then subsequent doses may be administered at home. The approved once-daily

(q.d.) OA dosage varies with country and/or patient age, but typically involves a 3-day dose-escalation from 100 to 300 IR per day, after which a 300 IR tablet is used daily until the end of the pollen season [37]. In the USA, patients aged 18–65 years begin treatment with the 300 IR dosage [38]. Treatment should be initiated around 4 months before the expected onset of the pollen season and must be maintained until the season ends [37,38].

Contraindications & special patient populations

OA is contraindicated in patients with severe, unstable or uncontrolled asthma and/or hypersensitivity to any of the inactive ingredients in the product. Treatment should be withheld in patients experiencing acute asthma exacerbations. Additionally, the US labeling advises that OA should not be used in patients with a history of any severe systemic allergic reaction or severe local reaction to SLIT, and in the EU summary of product characteristics, OA is also contraindicated in patients taking β -blockers and those with severe immunodeficiency, auto-immune disease or malignant disease [37,38].

In allergic patients with oral inflammation or wounds (including those following oral surgery or tooth extraction/loss), OA treatment should be stopped and only resumed once complete healing of the oral cavity has occurred. OA should only be administered during pregnancy if there is a clear need, and it should be used with caution in women who are breastfeeding [37,38].

Excipients (inactive drug additives)

The excipients used are mannitol, microcrystalline cellulose, croscarmellose sodium, colloidal anhydrous silica, magnesium stearate and lactose monohydrate [37,38].

Other AIT medications approved for the treatment of grass-pollen allergy

Besides OA, various aqueous and tablet SLIT therapies are available in the EU and other countries for the treatment of ARC [21], but only one other is also licensed in the EU and the USA: Grazax™/Grastek® (GRA) (ALK-Abello/Merck), a 75,000 SQ-T (standardized quality tablet units) oral lyophilized tablet for SLIT, containing a 1-grass-pollen allergen extract from timothy grass (*Phleum pratense*), approved in the USA in April 2014. A description of GRA efficacy and safety may be found in reference [39]. Using the unit of standardization of allergen extracts recognized by the US FDA (bioequivalent allergy unit [BAU]), OA is 9000 BAU, while GRA is 2800 BAU, equating to the former having over three-times more allergenicity than the latter [38,40]. Several of the other SLIT allergen preparations are named patient products and/or have only gained local marketing approval in a small number of countries [41].

The key difference between GRA and OA (apart from being 1-grass vs 5-grass-pollen preparations, respectively; see section 'Chemistry of the 5-grass-pollen tablet'), is that the former advocates perennial administration, unlike OA, which is only

taken from 4 months before the expected start of the pollen season until its end.

Chemistry of the 5-grass-pollen tablet

In total, 13 groups of allergens that demonstrate significant IgE cross-reactivity have thus far been identified from pollen of the Pooideae subfamily of grasses [42]. Grass allergens belonging to groups 1 (glycoproteins) and 5 (non-glycosylated proteins) are well characterized and constitute the major allergens, which account for more than 80% of the allergenic potential of grass-pollen [7,43]. Groups two and three constitute minor allergens, which are recognized by 40–60% of allergic patients [7].

The active substance within the 5-grass-pollen tablet consists of a purified and calibrated freeze-dried extract of pollen from sweet vernal grass (*Anthoxanthum odoratum*), cocksfoot/orchard grass (*Dactylis glomerata*), perennial rye grass (*Lolium perenne*), meadow grass (*Poa pratensis*) and timothy grass (*Phleum pratense*) [44]. A dosage of 300 IR equates to approximately 20–25 µg/ml of the group five major allergens [45].

There is a specific rationale justifying the use of allergens from multiple grass-pollens in the 5-grass-pollen tablet, instead of allergens from a single grass-pollen. A 5-grass-pollen extract better represents the natural exposure and sensitization conditions encountered by allergic patients, because the corresponding grass species are broadly distributed throughout North America and Europe, and polysensitization is common among patients [7,42]. Although high amino-acid sequence homology is found between Pooideae grass-pollens for group 1 and 5 allergens (90 and 55–80% homology, respectively), qualitative and quantitative differences exist in their expression between grass species [7,36,42]. Consequently, variations among allergic patients have been observed in the degree of sensitization toward both shared and species-specific epitopes from these allergens [7,36]. Moreover, a recent study highlighted that polysensitization toward grass-pollen allergens not only occurs at the IgE level, but also at the T-cell level, and Pooideae species-specific T-cell epitopes that are minimally cross-reactive exist among group 1 and 5 allergens [46]. The findings of this study imply that single-allergen immunotherapy may not cover the broad epitopic repertoire at the T-cell level, and therefore may not elicit Treg responses in allergic patients, or deplete the population of species-specific T cells that show minimal cross-reactivity, with a consequent failure to induce tolerance [46]. A study with GRA also reported cross-reactivity at the T-cell level [47], but this used an artificial system of two generated T-cell lines, and not T cells isolated from allergic patients (as in reference [46]); therefore, T cells specific for minimally cross-reactive epitopes may have been missed. A mixed grass-pollen extract is more likely to ensure that a broad and well-balanced panel of critical major and minor allergenic epitopes is present, whereas a single grass-pollen preparation would likely restrict the repertoire of allergenic epitopes to which a patient becomes desensitized [36,42]. Further clinical trials are needed to clarify whether differences in the degree of sensitization toward epitopes correlate with differences in the ability of SLIT to elicit immunotolerance.

Pharmacodynamics & mechanism of action

OA is used for the treatment of patients with specific IgE-mediated allergy symptoms, such as rhinitis with or without conjunctivitis caused by grass-pollen. Its pharmacodynamic effect is targeted at the immune system, to elicit an immune response against the allergen with which the patient is treated [37]. Recently, a better understanding of the immune mechanisms involved in allergen-specific SLIT has confirmed the pertinence of the sublingual route for induction of allergen-specific tolerance. The peculiar characteristics of the oral/lingual immune system mean that in the absence of danger signals, Langerhans cells, myeloid dendritic cells and macrophages located in oral tissues, tonsils and draining cervical lymph nodes are biased toward the induction of a suppressive/tolerogenic default response to antigen, rather than an inflammatory one [48]. This is facilitated by the induction of Th1 and IL-10-producing CD4⁺ Treg and an increase in blocking anti-inflammatory IgG and/or IgA antibodies [48]. Grass-pollen SLIT leads to a systemic competitive antibody response toward grass, and an increase in specific IgG [48]. Moreover, SLIT does not appear to cause IgE neosensitization to allergens for which the immune system is naïve before treatment [48].

Pharmacokinetics & metabolism

The majority of allergens in OA are a mixture of proteins and glycoproteins. There is limited, if any, release of intact allergens into the bloodstream [48], and they are thus not directly bio-available in the blood. No studies have been performed to investigate the pharmacokinetic profile and metabolism of OA.

Clinical efficacy of the 300 IR 5-grass-pollen tablet

The OA tablet has followed a well-defined clinical development plan, and its efficacy and safety for grass-pollen-allergy treatment has been demonstrated by more than 5 years of clinical and real-world experience. The efficacy of 5-grass-pollen tablet was evaluated in six randomized, double-blind, placebo-controlled clinical trials: VO34.04 (EU dose-finding study in adults) [45], VO56.07A (EU allergen exposure chamber study in adults) [49], VO52.06 (EU pediatric study in adolescents and children) [50], VO53.06 (EU/Canada long-term efficacy study in adults) [28,51], VO61.08 (US study in adults) [52] and VO60.08 (EU alternate regimen study in adults, adolescents and children) [53]. One additional study in adults, VO33.04DK [54], was designed to gather only safety and tolerability data. Across all Phase I–III clinical trials, a total of 2512 participants have been randomized to receive 5-grass-pollen tablet (n = 1514) or placebo (n = 998) in and outside Europe (TABLE 1).

Phase IIb/III: VO34.04 (EU dose-finding efficacy study in adults)

VO34.04 investigated the efficacy, safety and optimal dose of 5-grass-pollen tablet in adults having grass-pollen-induced ARC for at least 2 years. The primary efficacy measure was the Average Rhinoconjunctivitis Total Symptom Score (ARTSS), and secondary efficacy measures included the six individual AR

Table 1. Summary of 5-grass-pollen sublingual immunotherapy tablet Phase I–III clinical trials and design.

Study Phase	Design and objectives	Location	Population	Treatment	Exposed patients (n)	Treatment duration	Ref.
VO33.04DK I 2006	Single-center, randomized, double-blind, placebo-controlled Safety	Denmark	Patients allergic to grass-pollen Age 18–50 years	100–500 IR Placebo Total	23 7 30	2 weeks (omitting weekends for 10 treatment days in total)	[54]
VO34.04 IIb/III 2005	Pivotal, multicenter, multinational, randomized, double-blind, placebo-controlled Efficacy, dose-finding	10 EU countries: Austria, Bulgaria, Czech Republic, Denmark, France, Germany, Hungary, Italy, Slovakia, Spain	Patients with grass-pollen-related ARC with or without mild asthma Age 18–45 years	500 IR (4M) 300 IR (4M) 100 IR (4M) Placebo Total	160 155 157 156 628	~4 months pre-seasonally and ≥1 month co-seasonally	[45]
VO56.07A I 2007–08	Single-center, randomized, double-blind, parallel-group, placebo-controlled Efficacy, safety	Austria (allergen exposure chamber)	Patients with grass-pollen-related ARC without mild asthma Age 18–50 years	300 IR Placebo Total	45 44 89	~4 months	[49]
VO52.06 III 2007	Multicenter, multinational, double-blind, placebo-controlled Efficacy, safety	5 EU countries: Denmark, France, Germany, Poland, Spain	Patients with grass-pollen-related ARC with or without mild asthma Age 5–17 years	300 IR (4M) Placebo Total	139 139 278	~4 months pre-seasonally and ≥1 month co-seasonally	[50]
VO53.06 III 2007–11	Multicenter, randomized, double-blind, placebo-controlled Efficacy, safety	10 countries: Austria, Canada, Czech Republic, Denmark, France, Germany, Italy, Poland, Russia, Slovakia	Patients with grass-pollen-related ARC with or without mild asthma Age 18–50 years	300 IR (4M) 300 IR (2M) Placebo Total	207 207 219 633	5 years: ~4 months pre-seasonally and ≥1 month co-seasonally over 3 years, followed by 2 years without study treatment	[28,51]
VO61.08 III 2009	Pivotal, multicenter, randomized, double-blind, parallel-group, placebo-controlled Efficacy, safety	USA (51 sites)	Patients with grass-pollen-related ARC with or without mild asthma Age 18–65 years	300 IR (4M) Placebo Total	233 240 473	~4 months pre-seasonally and ≥1 month co-seasonally	[52]
VO60.08 III 2009	Multicenter, multinational, randomized, double-blind, placebo-controlled Efficacy, safety	5 EU countries: Czech Republic, France, Italy, The Netherlands, Spain	Patients with grass-pollen-related ARC Age 12–65 years	300 IR (2M) Placebo Total	188 193 381	~2 months pre-seasonally and ≥1 month co-seasonally	[53]

Subjects in the 300 IR (study VO34.04 and VO52.06) and the 500 IR (study VO34.04) treatment groups underwent a dose-escalation phase wherein a 100 IR dose was taken on the first day, then increased by 100 IR daily until the final randomized dose was reached.
2M or 4M, patients received active treatment starting 2 or 4 months, respectively, before the pollen season.
ARC: Allergic rhinoconjunctivitis; IR: Index of reactivity; SLT: Sublingual immunotherapy.

Table 2. Summary of 5-grass-pollen sublingual immunotherapy tablet efficacy from five Phase I–III clinical trials.

Study Phase	Primary end point	Treatment	Primary analysis set (n)	LS mean	LS mean difference vs placebo		p-value vs placebo [†]	Ref.
					Absolute point estimate (95% CI)	Relative point estimate (%)		
VO34.04 EU study in adults IIb/III	ARTSS	500 IR (4M)	143	3.74	-1.22 (-1.91, -0.53)	-24.7	0.0006	[45]
		300 IR (4M)	136	3.58	-1.39 (-2.09, -0.69)	-28.2	0.0001	
		100 IR (4M)	142	4.72	-0.26 (-0.95, 0.43)	-5.3	0.4606	
		Placebo	148	4.93				
VO56.07A Allergen-exposure chamber study in adults I	ARTSS	300 IR	45	4.85	-1.97 (-2.99, -0.94)	-29.3	0.0003	[49]
		Placebo	44	6.87				
VO52.06 EU pediatric study III	ARTSS	300 IR (4M)	131	3.25	-1.13 (-1.80, -0.46)	-25.5	0.0010	[50]
		Placebo	135	4.51				
VO53.06* Long-term efficacy study in adults III	AAdSS	300 IR (4M)	149	3.39	-1.82 (-2.61, -1.02)	-34.9	<0.0001	[28,51]
		300 IR (2M)	147	3.25	-1.96 (-2.76, -1.16)	-37.6	<0.0001	
		Placebo	165	5.21				
VO61.08 US study in adults III	Daily CS [§]	300 IR (4M)	208	0.32	-0.13 (-0.19, -0.06)	-28.2	0.0003	[52]
		Placebo	228	0.45				

2M or 4M, patients received active treatment starting 2 or 4 months, respectively, before the pollen season.
[†]Based on absolute point estimate of LS mean difference.
^{*}Year 3 results are presented.
[§]Daily CS is derived from the RTSS and RMS and gives equal weight to symptoms and medication use. This score is conventionally expressed on a scale from 0 to 3 and calculated per day for each patient as: daily CS = (daily RTSS/6 + daily RMS)/2.
AAdSS: Average Adjusted Symptom Score; ARC: Allergic rhinoconjunctivitis; ARTSS: Average rhinoconjunctivitis Total Symptom Score; CS: Combined Score; IR: Index of reactivity; LS: Least squares; RMS: Rescue Medication Score; RTSS: Rhinoconjunctivitis Total Symptom Score; SLIT: Sublingual immunotherapy.

symptom scores from the ARTSS, symptomatic medication use, QoL (assessed using the Rhinoconjunctivitis Quality of Life Questionnaire [RQLQ]) and safety [45].

In the intent-to-treat (ITT) population (n = 628), mean ARTSS was significantly lower throughout the pollen season in the 300 and 500 IR tablet groups, compared with the placebo groups, irrespective of comorbid mild asthma or sensitization status (300 IR: 3.58 ± 2.976 ; 500 IR: 3.74 ± 3.142 ; placebo: 4.93 ± 3.229 ; $p < 0.0001$ and 0.0006 for 300 IR and 500 IR, respectively vs placebo) (TABLE 2). Median improvements in RTSS were 37 and 35% for the 300 and 500 IR tablet groups, respectively, compared with placebo. Similar results were observed for the per-protocol population. Analysis of all secondary efficacy measures confirmed the efficacy of the 300 and 500 IR doses. In these two groups, all individual nasal and ocular symptoms were significantly improved versus placebo, including nasal congestion, which is a symptom not normally relieved by H₁-antihistamines [45].

Usage of symptomatic medication was significantly lower in patients receiving 300 IR 5-grass-pollen tablet therapy (46%), compared with their counterparts taking placebo ($p = 0.019$). The 300 IR 5-grass-pollen tablet therapy also significantly improved QoL; overall RQLQ scores were highly significantly different between the 300 and 500 IR tablet groups versus placebo, at the peak of the pollen season. The risk–benefit ratio favored the use of the 300 IR dose in the clinical setting [45].

A *post hoc* analysis of this study confirmed the efficacy of the 300 IR 5-grass-pollen tablet in all patient subgroups, irrespective of symptom severity, sensitization status (mono-/polysensitization) or presence of comorbid mild asthma [55]. In a subsequent *post hoc* analysis, the daily Combined Score (CS) (a measure that assigns equal weighting to symptom scores and symptom-relieving medication use) was calculated [29,56]. The least squares (LS) mean daily CS was 29.6% lower in the 300 IR tablet group than the placebo group (0.5 vs 0.7, respectively; $p < 0.0001$) [29,56].

Phase I: VO56.07A – allergen-exposure chamber study (onset of action in adults)

VO56.07A assessed the efficacy and onset of action of q.d. 300 IR 5-grass-pollen tablet therapy in adults with grass-pollen-induced ARC (for at least the two previous pollen seasons), following an allergen challenge (concentration of allergen 1450–1500 pollen grains/m³, the level typically found in the Austrian countryside at a height of 1.5 m during pollen peaks) in an allergen-exposure chamber. Patients underwent allergen challenge with grass-pollen before treatment, and again after week 1 and months 1, 2 and 4 of treatment. The primary efficacy measure was ARTSS after 4 months of treatment or at end point. Secondary efficacy measures included nasal airflow, nasal secretion weight and cutaneous reactivity [49].

In the ITT population (n = 89), the 300 IR 5-grass-pollen tablet group had a significantly lower ARTSS after 4 months of treatment (or at study end point) versus placebo, equating to a relative mean improvement of 29.3% (TABLE 2). These findings were confirmed in the per-protocol population (n = 83) and a separate sensitivity analysis. Regarding onset of action in the 300 tablet group, ARTSS decreased incrementally from week 1 (7.40 ± 2.68), achieving a significant treatment effect after the first month ($p = 0.0042$; ARTSS: 5.89 ± 2.43), which was maintained at 2 ($p = 0.0203$; ARTSS: 5.09 ± 2.09) and 4 months ($p = 0.0007$; ARTSS: 4.85 ± 2.00) [49].

Phase III: VO52.06 (EU pediatric study in adolescents & children)

VO52.06 investigated the efficacy and safety of 300 IR 5-grass-pollen tablet therapy in children and adolescents having grass-pollen-induced ARC for at least 2 years, confirmed by means of a positive skin prick test response [50].

Treatment was initiated 4 months before the predicted pollen season and continued throughout the season. The primary efficacy measure was the ARTSS, with secondary efficacy measures including symptomatic medication intake, individual symptom scores from the ARTSS and safety [50]. In a subsequent *post hoc* analysis, the daily CS was also calculated [56].

Compared with placebo, 300 IR 5-grass-pollen tablet was effective over the whole pollen season ($p = 0.0010$) and at the pollen peak ($p = 0.0009$). In the ITT population (n = 266; 12 randomized patients [4.3%] were excluded because they withdrew before the pollen season and therefore had no efficacy assessment), the ARTSS for patients receiving active treatment was highly significantly different to that of the placebo group ($p = 0.001$) (TABLE 2). In both the younger (5–11 years) and older (12–17 years) age groups, the ARTSS score was lower in patients receiving 300 IR 5-grass-pollen tablet than in those receiving placebo. The adjusted mean difference between the two groups was also significant for both nasal ($p = 0.0183$) and ocular ($p < 0.0001$) symptoms. The 300 IR 5-grass-pollen tablet group showed a mean improvement in ARTSS of 28.0% compared with placebo, and a median improvement of 39.3%. Analysis of the per-protocol population confirmed these findings. Significant differences between the 300 IR 5-grass-pollen

tablet and placebo groups were also observed in use of symptomatic medication score ($p = 0.0064$) and mean proportion of days using symptomatic medications during the pollen season (35.4 vs 46.5% for the 300 IR tablet and placebo groups, respectively; $p = 0.0146$). Mild asthma or sensitization status had no significant effect on the efficacy results [50]. A *post hoc* analysis of study data using daily CS further confirmed the efficacy of 300 IR 5-grass-pollen tablet in this pediatric population [29,56]. The LS mean difference in daily CS between patients using 300 IR 5-grass-pollen tablet and placebo was -0.19 [95% CI: $-0.29, -0.08$], equating to a significant relative difference of 30% ($p = 0.0005$) [29,56].

Phase III: VO53.06 (EU/Canada long-term efficacy study in adults)

VO53.06 investigated the sustained efficacy of two dosing regimens (q.d. treatment for 2 or 4 months) of a pre- and co-seasonal 300 IR 5-grass-pollen tablet in adults with seasonal grass-pollen-induced ARC for at least the two previous pollen seasons. There was no titration phase (in contrast to the recommended posology in the OA labeling; see section 'Introduction to 300 index of reactivity 5-grass-pollen tablet'). The primary efficacy measure was the Average Adjusted Symptom Score (AAdSS), assessed for the third pollen season. Secondary efficacy measures included ARTSS, individual symptom scores, Average Rescue Medication Score (ARMS), overall RQLQ score and safety [28,51].

In total, 633 patients were randomized to placebo (n = 219), or a pre- and co-seasonal treatment with 300 IR 5-grass-pollen tablet, occurring either 2 or 4 months before and then during the pollen season (n = 207 in both groups). Over the third pollen season, mean AAdSS was reduced by 37.7 and 34.8% in the 2- and 4-month active treatment groups, respectively, compared with the placebo group ($p < 0.0001$ for both) (TABLE 2). Reductions were also observed in ARTSS, individual symptom scores and ARMS, with a marked improvement in QoL for both 300 IR 5-grass-pollen tablet treatment groups versus placebo [51].

Overall, 435 and 377 patients contributed to the pollen season 4 and 5 efficacy analyses, respectively [28,30]. Both active treatment groups showed statistically significant differences compared with placebo in LS mean AAdSS, and statistically significant differences versus placebo in ARTSS, ARMS and overall RQLQ score. In the fourth pollen season (i.e., first post-treatment year), the LS mean difference in AAdSS continued to significantly favor 300 IR 5-grass-pollen tablet over placebo (-1.14 ; 95% CI: $-2.03, -0.26$; $p = 0.0114$) [28], with this trend continuing into the fifth pollen season (i.e., post-treatment year 2) [30]. A *post hoc* analysis showed that daily CS was significantly improved across all 5 years of the study ($p \leq 0.05$) in the group of patients who used 300 IR 5-grass-pollen tablet for the first three pollen seasons, according to a 4-month pre- and co-seasonal schedule, compared with their counterparts using placebo [30]. At years 4 and 5 (i.e., the first and second post-treatment years), the LS mean relative

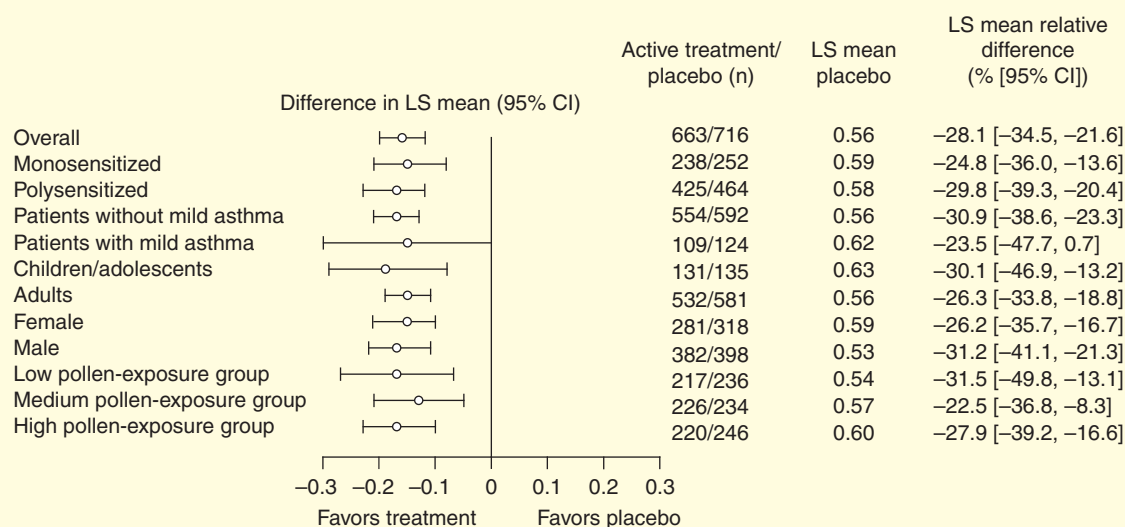


Figure 1. Pooled efficacy analysis of the 5-grass-pollen sublingual immunotherapy tablet: Daily Combined Score overall and in subpopulations of interest [30].

CI: Confidence interval; LS: Least squares.

differences in daily CS for patients previously treated with OA versus placebo were -25.3% ($p = 0.0103$) and -28.1% ($p = 0.0478$), respectively [30]. There was no impact of mild asthma or sensitization status on the efficacy results throughout the study. This long-term study demonstrates the sustained effect of 300 IR 5-grass-pollen tablet therapy on maintenance of improvement in ARC symptoms, reduced need for symptomatic medications and improvement in QoL, in a broad group of patient types, including those with mild asthma or who are polysensitized [28].

Phase III: VO61.08 (US study in adults)

VO61.08 investigated the efficacy and safety of 300 IR 5-grass-pollen tablet therapy in adults with documented grass-pollen-related ARC (mean duration: 22.3–23.4 years). Patients aged 18–65 years were randomized to 300 IR 5-grass-pollen tablet or placebo. The primary efficacy measure was reduction in daily CS (a scale of 0–3), taking into account ARC symptoms and use of symptomatic medications [52].

In total, 473 patients were randomized to 300 IR 5-grass-pollen tablet ($n = 233$) or placebo ($n = 240$). Throughout the pollen period, the mean daily CS was consistently lower in the active treatment group than the placebo group, and reflected the grass-pollen count. Overall, a statistically significant reduction of LS mean daily CS was observed with 300 IR 5-grass-pollen tablet versus placebo (0.32 vs 0.45; $p < 0.001$), equating to a relative difference of 28.2% (TABLE 2). Sensitization status and presence of mild asthma were not significant covariates, indicating that they did not affect the primary efficacy findings [52].

Subgroup analyses of special populations

Pooled efficacy data from clinical trials were analyzed in subsets of patients according to their sensitization status (mono- or

polysensitized), presence of mild asthma, age (children/adolescents or adults), gender and level of pollen exposure (low, medium or high). Apart from asthma status, each of the pooled efficacy analyses demonstrated statistically significant differences in daily CS between the 5-grass-pollen tablet and placebo, irrespective of covariate. In the comparatively small number of patients with mild asthma, the differences were numerically in favor of 5-grass-pollen tablet, but did not reach statistical significance (FIGURE 1) [30].

A *post hoc* analysis of studies VO34.04 (EU efficacy study in adults), VO52.06 (EU pediatric study) and VO53.06 (EU/Canada long-term study in adults), which stratified patients according to symptom severity (based on the placebo population symptom score in each center), highlighted that 5-grass-pollen tablet therapy is able to elicit highly clinically relevant improvements in those patients suffering from the most severe symptoms [57]. Pooled centers were ranked from lowest to highest mean considered scores (AAdSS or ARTSS) in the placebo group and grouped into three clusters, comprising approximately one-third of patients. The grouping of centers was pre-specified but retrospectively assigned, once the placebo results for each center were known for that particular pollen season. Improvements in combined symptom scores in patients using 5-grass-pollen tablet therapy ranged from 27 to 37% versus placebo, representing relative differences beyond what is normally reported for symptomatic medications [57], and which are markedly above the minimal clinically relevant difference in efficacy versus placebo of 20% that is recommended by the World Allergy Organization [58].

Post-marketing surveillance studies

The worldwide post-marketing experience with OA includes more than 20 million doses given to more than 110,000 allergic patients.

Non-interventional study in Germany

This was a multicenter, prospective, open-label, non-controlled, non-interventional study conducted at 327 study centers in Germany from September 2010 to October 2012 to investigate the efficacy and tolerability of 2 consecutive years of a pre-/co-seasonal treatment regimen with OA in patients with grass-pollen-induced ARC (mean duration: 7.6–8.3 years). Patients aged 4–75 years (mean age 28 years) ($n = 1482$) rated their symptoms of rhinitis, conjunctivitis and/or mild asthma according to a CS for severity (0 = none, 3 = severe) and frequency (0 = never, 4 = very often), and severity scores for rhinitis and conjunctivitis were pooled to produce a combined rhinoconjunctivitis (RC) score (0 = none, 6 = severe) [29,59–61].

In total, 84% of patients reported use of symptomatic medications during the grass-pollen season preceding entry into the study, which decreased significantly to 52 and 43% in the first and second seasons of OA treatment, respectively ($p < 0.001$). Significant decreases in mean RC scores were noted in the first and second grass-pollen seasons (51 and 64%, respectively), compared with the preceding season ($p < 0.001$). Patients with comorbid mild asthma (38%; $n = 522$) had a significant decrease ($p < 0.001$) in mean asthma symptom score (1.42 ± 1.48 and 1.08 ± 1.37 in the first and second year of treatment) versus baseline (3.56 ± 1.58), equating to a 60 and 70% decrease for years 1 and 2, respectively, versus the previous year. After the second year of OA treatment, 94% of patients reported an improvement in health status, which was corroborated by their treating physician [29,61].

Of the patients who completed the entire study period ($n = 652$), 82% were considered to have full symptom control (RC score < 1) [29,60]. Subgroup analysis of the pediatric population in the study ($n = 449$; 248 children aged 4–11 years and 201 adolescents aged 12–17 years) showed comparable decreases in symptomatic medication use and RC score with OA therapy, with 96 and 97% of children and adolescents reporting an improvement in health status after the second pollen season [29,59]. At baseline, 88.3% of children and 84.6% of adolescents used medications, decreasing to 56.5 and 48.0% (children) and 55.6 and 40.3% (adolescents) at years 1 and 2 of OA treatment, respectively. In children/adolescents, RC scores were 1.93/1.97 and 1.39/1.39 in the first and second year of treatment versus 4.10/4.05 at baseline [59]. In the subgroup of children and adolescents with comorbid mild asthma ($n = 166$), OA therapy was associated with significant decreases in asthma and RC symptom scores, and symptomatic medication use, for both pollen seasons versus the preceding season [29,59].

SMILE study in Spain

SMILE was a multicenter, observational, cross-sectional study carried out in Spain at the end of the 2012 grass-pollen season, to gather data on the clinical characteristics of patients previously naïve to OA therapy. All patients had uncontrolled moderate/severe ARC while under symptomatic therapy, and received OA therapy for the first time, according to the

recommended pre-/co-seasonal regimen. Adult patients (mean age: 33.9 ± 11.5 years) ($n = 226$) were included in the study, of whom 55% had mild asthma and 60% were polysensitized. QoL and satisfaction with treatment were assessed using two validated instruments, the RQLQ and the Satisfaction Scale for Patients Receiving Allergen Immunotherapy [29,62,63].

At baseline, 92% of patients had persistent moderate/severe ARC, according to Allergic Rhinitis and its Impact on Asthma criteria. Following OA therapy (mean treatment duration: 4.9 months), this decreased to 30 and 49% of patients had transitioned to mild ARC, with corresponding improvements noted in their QoL. In total, 71–85% of patients reported an improvement in their symptoms, compared with previous grass-pollen seasons: 44% no longer experienced sleep disturbances, 67% reported that their daily activities were now unaffected and 64% no longer had work impairments. The percentage of patients using oral H_1 -antihistamines and nasal corticosteroids decreased from 92 and 77% at baseline to 62 and 28%, respectively, following OA therapy (equating to 33 and 54% fewer patients using oral H_1 -antihistamines and nasal corticosteroids, respectively). Of those patients still requiring medications for symptom control, 80% of H_1 -antihistamine users and 69% of nasal corticosteroid users reported decreased consumption, compared with prior to OA therapy. Patients were highly satisfied with OA therapy, registering a global Satisfaction Scale for Patients Receiving Allergen Immunotherapy score of 62 ± 15 points (on a scale of 16–80 points, where higher scores equate to greater satisfaction) [29,62,63].

Safety & tolerability

Across the clinical development program, 5-grass-pollen tablet showed a favorable safety profile and was generally well tolerated. Most AEs during treatment were mild or moderate in severity, with the most common (reported in $\geq 5\%$ of patients) being oral pruritus, throat irritation, ear pruritus, mouth edema, tongue pruritus, cough and oropharyngeal pain (TABLE 3). The majority of AEs showing a differing incidence with placebo were local reactions related to the route of administration, particularly oral pruritus and throat irritation. No death or intensive care unit admission was reported in any patient receiving 5-grass-pollen tablet, and no reports of 'anaphylactic shock' or 'anaphylaxis', or relevant effects on vital signs or laboratory parameters were observed. Tolerability improves with continued use of 5-grass-pollen tablet; in the VO53.06 long-term clinical trial, the incidence and severity of treatment-emergent AEs reported by adults using 300 IR 5-grass-pollen tablet for three consecutive grass-pollen seasons incrementally decreased during the second and third treatment seasons, compared with the first season [51].

Phase I: VO33.04 DK (safety study in adults)

In this study, subjects were allocated to four treatment groups: for active treatment, groups 1 and 2 received incremental doses of 100, 200, 300, 400 and 500 IR (increasing every second day in group 1 and daily in group 2, who remained on the

Table 3. Summary of 5-grass-pollen sublingual immunotherapy tablet adverse drug reactions in adults from clinical trials [37].

MedDRA SOC	Frequency (%)			
	Very common (≥1/10)	Common (≥1/100 and <1/10)	Uncommon (≥1/1000 and <1/100)	Rare (≥1/10,000 and <1/1000)
Infections and infestations		Nasopharyngitis, rhinitis	Oral herpes, otitis	
Blood and lymphatic system disorders			Lymphadenopathy	
Immune system disorders			Hypersensitivity, oral allergy syndrome	
Psychiatric disorders			Depression	
Nervous system disorders	Headache		Dysgeusia, somnolence, dizziness	Anxiety
Eye disorders		Eye pruritus, conjunctivitis, lacrimation increased	Eye redness, eye edema, dry eye	
Ear and labyrinth disorders		Ear pruritus	Ear discomfort	
Vascular disorders				Flushing
Respiratory, thoracic and mediastinal disorders	Throat irritation	Asthma, AR (nasal congestion, sneezing, rhinorrhea, nasal discomfort), cough, oropharyngeal pain, pharyngeal edema, sinus congestion, dyspnea, dysphonia, dry throat, oropharyngeal blistering, oropharyngeal discomfort	Pharyngeal hypoesthesia, throat tightness, wheezing, laryngeal edema	
Gastrointestinal disorders	Oral pruritus	Abdominal pain, diarrhea, vomiting, mouth edema, tongue pruritus, lip edema, paresthesia oral, dyspepsia, tongue edema, hypoesthesia oral, stomatitis, lip pruritus, oral discomfort, nausea, glossodynia, dry mouth, dysphagia	Oral pain, gingivitis, cheilitis, gastritis, glossitis, salivary gland enlargement, gastroesophageal reflux, tongue disorder, salivary hypersecretion, mouth ulceration, esophageal pain, palatal edema, oral disorder,odynophagia, eructation	
Skin and subcutaneous tissue disorders		Urticaria, pruritus, atopic dermatitis	Angioedema, rash, acne	Face edema
General disorders and administration site conditions		Chest discomfort	Lump feeling in throat, asthenia, influenza-like illness	
Investigations				Eosinophil count increased
Injury, poisoning and procedural complications			Excoriation	

Within each frequency category, serious reactions are presented first. Overall, the safety profile in the pediatric population is similar to that of adults. The following reactions listed above were reported at a higher frequency in the pediatric population than in adults: cough, nasopharyngitis, mouth edema (very common), oral allergy syndrome, cheilitis, glossitis, lump feeling in throat, ear discomfort (common). Additionally, the following reactions were reported in children and adolescents who received OA: tonsillitis, bronchitis (common), chest pain (uncommon).

AR: Allergic rhinitis; MedDRA: Medical Dictionary of Regulatory Activities; OA: Oralair®; SLIT: Sublingual immunotherapy; SOC: System Organ Class.

500 IR dose once this was reached), while groups 3 and 4 received a constant dose of 300 or 500 IR, respectively. Placebo was administered to two subjects in groups 1, 2 and 4, and one subject in group 3. Safety assessments included reporting of AEs, assessment of vital signs and clinical laboratory tests [54].

Five-grass-pollen tablet was generally well tolerated, with the majority of AEs occurring on the first day of treatment. Most AEs were mild to moderate in severity and related to the site of administration, and resolved rapidly without the need for intervention. Two treatment-related serious AEs consistent with laryngopharyngeal reactions occurred on the first day of treatment in group 4, within 5 min of dosing. Symptoms were treated with corticosteroids and resolved without sequelae. No serious systemic AEs were reported. There were no relevant effects on vital signs or laboratory parameters [54].

Phase IIb/III: VO34.04 (EU dose-finding efficacy study in adults)

In the safety population (n = 628), a total of 384 patients reported treatment-emergent AEs, comprising 68.8, 62.6, 64.4 and 48.7% of patients receiving 100, 300 and 500 IR 5-grass-pollen tablet or placebo, respectively. The most frequently reported AE in patients receiving 5-grass-pollen tablet was oral pruritus (19.7, 25.8 and 25.6% of 100, 300 and 500 IR dose-treated patients vs 5.1% in the placebo group). No treatment-related serious AEs were reported. The percentage of patients stopping their treatment prematurely due to an AE was 3.8, 5.2 and 6.9% (100, 300 and 500 IR dose groups, respectively) versus 0% of patients taking placebo. Overall treatment compliance was 87.7% for patients taking 300 IR 5-grass-pollen therapy [45].

A complementary analysis of study VO34.04 (study VO40.05) confirmed the favorable safety and tolerability of 300 IR 5-grass-pollen tablet, irrespective of the presence of comorbid mild asthma, mono- or polysensitization to grass-pollen allergens or AR symptom severity [55].

Phase III: VO52.06 (pediatric study in adolescents & children)

In this study, AEs were generally mild or moderate in intensity, and in keeping with the known safety profile for the 5-grass-pollen tablet. Treatment-emergent AEs occurred in 84.9 and 82.0% of patients receiving 5-grass-pollen tablet or placebo, respectively, and no treatment-related serious AEs were noted. The most frequently reported AEs were oral pruritus, mouth edema and throat irritation, in 32.4, 12.9 and 7.9% of actively treated patients versus 1.4, 0 and 5.0% of placebo-treated patients. Treatment discontinuation due to AEs occurred in 5.3 and 1.5% of patients using 5-grass-pollen tablet or placebo, respectively [50,64].

Notably, the incidence of treatment-emergent AEs remained comparable when split by age group, occurring in 86.2% of children (aged 5–11 years) and 82.7% of adolescents (aged

12–17 years) on active treatment, with corresponding values of 82.4 and 81.5%, respectively, for patients taking placebo [64].

Phase III: VO61.08 (US study in adults)

Treatment-related AEs occurred in 54.9 and 22.5% of patients in the 300 IR 5-grass-pollen tablet and placebo groups, respectively. Five-grass-pollen tablet therapy was well tolerated, with the most frequently reported AEs being oral pruritus, throat irritation and nasopharyngitis. No treatment-related serious AEs were reported. There were no deaths, cases of anaphylaxis, nor exacerbations of comorbid mild asthma related to 5-grass-pollen tablet use and no actively treated participant received epinephrine. In total, 4.7% of patients on active treatment discontinued due to drug-related, treatment-emergent AEs, which were mostly local application-site reactions of mild or moderate severity [52].

Post-marketing: non-interventional studies in Germany

Over the 2 years of this non-interventional study, OA treatment was well tolerated, with a total of 406 treatment-related AEs occurring in 210 patients (14%), and 33 treatment-related serious AEs occurring in 7 patients (0.5%). The most frequently reported AEs were throat irritation (2.9%), oral pruritus (2.6%), tongue or mouth edema (1.7%), dyspnea (1.4%) and nausea (0.9%). The majority of AEs occurred during the first year of treatment. At study end, 97.7% of patients rated the tolerability of OA therapy as 'very good' or 'good', with only 0.9% reporting 'poor' tolerability [61].

Post-marketing Authorization Safety Study: adults in Germany

At the request of the German regulatory authorities, a multicenter, non-randomized, prospective, open-label, non-interventional Post-marketing Authorization Safety Study (PASS) was performed between September 2008 and December 2009 at 354 study centers across Germany. Patients with grass-pollen-induced AR and/or conjunctivitis (n = 899; 808 adults, 91 children and adolescents) were enrolled and treated with OA according to a 4-month pre- and co-seasonal regimen, as stated in product labeling. The safety and tolerability of OA treatment was assessed over one treatment period (mean duration: 191.2 days), during which 320 patients (35.6%) reported AEs. The most commonly reported AEs were categorized under the Medical Dictionary of Regulatory Activities System Organ Classes for gastrointestinal disorders (27.5%; mainly oral paresthesia: 10.9%, oral pruritus: 6.9% and mouth edema: 5.3%), respiratory, thoracic and mediastinal disorders (13.8%; mainly throat irritation: 7.7%) and skin and subcutaneous disorders (3.2%; mainly pruritus: 1.9%). In total, 85 (9.5%) patients prematurely withdrew due to AEs, with the most common reason being mouth edema. In patients on active OA therapy, the reported adherence was 95% [30].

PASS: children & adolescents in Germany

This second PASS was a multicenter, prospective, open-label, observational study performed between November 2009 and

September 2010 at 206 study centers in Germany. Overall, children and adolescents aged 5–17 years with grass-pollen-induced AR and/or conjunctivitis (mean time since diagnosis: 3.2 years) ($n = 829$) were enrolled and treated with OA according to a 4-month pre- and co-seasonal regimen. As per the 2008–09 PASS in adults, the safety and tolerability of OA was assessed over one treatment period (mean duration: 190.2 days). The reported adherence with OA therapy was 98%, and safety data were available for 796 patients [30].

During the treatment period, 218 patients (27.4%) reported AEs, of which the majority was mild or moderate in severity. The most commonly reported AEs were throat irritation ($n = 114$), oral paresthesia ($n = 49$), oral pruritus ($n = 39$) and mouth edema ($n = 37$), categorized under the Medical Dictionary of Regulatory Activities System Organ Classes for gastrointestinal disorders (19.8%), respiratory, thoracic and mediastinal disorders (12.3%) and skin and subcutaneous disorders (2.3%) [30]. Serious AEs were reported in 6 patients (4 children and 1 adolescent), and 1 case of Quincke's edema of the lips, associated with hand and ear pruritus, occurred at day 26 in a boy aged 10 years, which was treated with corticosteroids per rectum, without the need for epinephrine use, and resolved within a day. The patient had a medical history of stable and well-controlled mild asthma and had undergone SCIT between October 2008 and January 2009, which had been discontinued due to the appearance of angioedema (and therefore, he could be considered an unsuitable candidate for SLIT). In this study, no deaths were reported, and 72 patients (9.6%) prematurely withdrew due to AEs, most commonly complaining of throat irritation. Nevertheless, tolerability was rated as 'good' or 'very good' by the majority of patients (84.7%), parents (87.0%) and clinicians (89.7%).

Health economics profile

In an economic analysis of 20 double-blind, placebo-controlled randomized trials identified via a systematic literature review, in which OA, GRA or SCIT was used for the treatment of grass-pollen-induced seasonal AR, OA showed at least non-inferior efficacy and comparable safety versus SCIT and GRA, at a lower annual cost [65]. During the first year of therapy, OA was associated with cost savings of \$2471, \$948 and \$1168 (Canadian) versus year-round SCIT, seasonal SCIT and GRA, respectively [65].

A separate evaluation was performed in Germany of the costs, outcomes and cost-effectiveness of 3-year treatment with symptomatic therapy (loratadine and/or budesonide) alone (standard of care) or in combination with OA, GRA or Alutard® (ALD; ALK-Abello, Hørsholm, Denmark; a 100,000 standardized quality units/ml depot preparation for SCIT, containing a 1-grass-pollen allergen extract from timothy grass [*Phleum pratense*] adsorbed to alum). A meta-analysis of randomized controlled trials for the three treatment regimens was also conducted to determine their effectiveness, relative to standard of care, for reducing RC symptom scores and increasing the number of symptom-free days. The findings suggested

that OA is cost-effective, relative to GRA, ALD and symptomatic medication [66]. Relative to symptomatic therapy, the predicted cost-utility ratio of OA was €14,728 per quality-adjusted life-year (QALY), with incremental costs of €1356 and incremental QALYs of 0.092 [66]. Meanwhile, in comparison to GRA or ALD, estimated incremental cost savings with OA were €1142 and €54, respectively, and corresponding incremental QALYs were 0.015 and 0.027. However, sensitivity analyses showed that model outcomes may have been affected by uncertainty surrounding treatment efficacy estimates [66].

A *post hoc* analysis of data from the VO34.04 and VO53.06 clinical trials used the AAdSS to compare AR treatment with OA versus placebo, and its cost-effectiveness [67]. A clinically significant improvement was a gain of ≥ 1.45 points in the AAdSS. In comparison to placebo, results indicate that OA is a cost-effective treatment option for adults with AR and a medium or high AAdSS, providing a benefit of 0.127 or 0.143 QALYs, respectively, with corresponding costs of €1024 and €1035 per QALY [67]. These findings may have important implications when deciding on the most appropriate management strategy for patients with AR who manifest moderate-to-severe symptoms.

Conclusion

OA is a q.d. pre- and co-seasonal 5-grass-pollen sublingual tablet that has been shown to be highly effective in controlling the symptoms of ARC, and reducing the need for symptomatic medication. It is effective from the first pollen season in all types of patients with ARC, including those with comorbid mild asthma, irrespective of mono- or polysensitization status and symptom severity. OA use for three pollen seasons has been shown to provide a sustained benefit in terms of symptom control and QoL, for at least 2 years after discontinuation of treatment. It has an excellent safety and tolerability profile in adults, adolescents and children and can be conveniently administered at home after the first dose. Compared with treatment with symptomatic medications, SCIT, GRA or ALD, OA appears to be a cost-effective therapy for AR/ARC.

Expert commentary

The clinical efficacy of OA in ARC is well-established through a large number of studies in adults and children, using a scheme of pre- and co-seasonal administration. Results from these studies are all remarkably consistent. The efficacy of OA is evident from the first pollen season via an improvement in clinical symptoms, decreased use of rescue medication, and improved QoL across patients aged ≥ 5 years. This favorable efficacy is maintained over successive pollen seasons and persists for at least two seasons after OA treatment is discontinued.

OA has a very good safety profile. AEs are generally mild or moderate in severity and lead only infrequently to treatment discontinuation. Furthermore, AEs tend to decline in frequency and severity over time, and with repeated treatment, during the second or third seasons.

Future research in the field will further confirm the broad benefits of OA therapy, and is expected to include studies investigating adherence rates of patients using OA over successive pollen seasons, improvement in QoL with OA therapy, and evaluation of OA efficacy in patients with mild to moderate pollen asthma. Further pharmacoeconomic analysis should also demonstrate the cost-effectiveness of OA treatment.

Five-year view

Stallergenes is planning to conduct two new studies as part of the clinical trials program for OA. The current US labeling has a lower age-limit restriction, because the pivotal US Phase III trial was conducted in adults aged 18–65 years (study VO61.08). Therefore, a new trial will be conducted in the EU, specifically in a pediatric population aged 5–9 years. A post-marketing study will be conducted in children, adolescents and adults aged 10–65 years.

Results are expected from a multicenter, international, observational study of OA currently underway in 10 countries, with the aim of following-up QoL for up to 5 years in patients with ARC. Several hundred patients with grass-pollen-induced ARC are expected to be recruited during the 2014–15 grass-pollen seasons for baseline data collection. Patients starting SLIT with OA will then be followed for up to 5 years (i.e., during and

after their OA treatment), with generic and specific self-administered health-related QoL questionnaires (the 12-Item Short-Form Health Survey and RQLQ), completed at home during the grass-pollen seasons.

Information resources

For more information about OA, please refer to the journal articles in the reference list marked as • ('of interest') or •• ('of considerable interest'), as well as the Stallergenes (www.stallergenes.com/en/stallergenes-group) and Oralair® (www.oralair.com) websites.

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Key issues

- Oralair® (OA) (Stallergenes, Antony, France) is a once-daily pre- and co-seasonal 5-grass-pollen sublingual tablet that is highly effective in controlling the symptoms of allergic rhinoconjunctivitis, and reducing the need for symptomatic medication.
- OA is effective from the first pollen season in all types of patients with allergic rhinoconjunctivitis, including those with comorbid mild asthma, irrespective of mono- or polysensitization status and symptom severity.
- OA use for three pollen seasons provides a sustained benefit in terms of symptom control and QoL, which is maintained for at least 2 years after discontinuation of treatment.
- OA has an excellent safety and tolerability profile in all age groups, and can be conveniently administered at home after the first dose.
- OA is a cost-effective option for the treatment of grass-pollen-induced AR, relative to symptomatic medications, subcutaneous immunotherapy and other sublingual immunotherapy.

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