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Pollinex[®] Quattro: a novel and well-tolerated, ultra short-course allergy vaccine

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Pollinex[®] Quattro is a novel, ultra short-course vaccine for treatment of seasonal allergic rhinitis from grass, tree or ragweed pollen allergy. Its unique formulation combines chemically modified allergens adsorbed onto a L-tyrosine depot to enhance tolerability with the novel adjuvant, monophosphoryl lipid A, to improve efficacy. Controlled clinical studies indicate that four preseasonal injections with grass or tree formulations significantly reduce rhinoconjunctivitis symptoms and medication use, as well as elevate allergen-specific immunoglobulin G and blunt elevation of immunoglobulin E upon allergen exposure. Postmarketing surveillance studies indicate similar clinical outcomes. In all cases, the allergy vaccine was well tolerated with minimal local reactions, while systemic reactions were rare and mild. Results from recent investigational trials with grass and ragweed formulations are consistent with previous efficacy and safety outcomes, and will be used toward product registration in North America.

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Pollinex[®] Quattro (PQ) is an ultra short-course therapeutic allergy vaccine (AV) provided in standardized allergen dose regimens for the treatment of allergy to grass, tree or ragweed pollens. PQ represents the next generation of AVs, which combine immunochemical innovations to improve patient safety, efficacy and compliance. Based on this formulation platform and therapeutic regimen, PQ is currently undergoing clinical trials for product registration in a number of jurisdictions worldwide. In this paper, PQ will be profiled by putting the vaccine into historical and scientific context with comparison to traditional AV formulations and therapeutic practices; clinical efficacy and tolerability data from both published papers and preliminary findings from recent investigational clinical trials will be reviewed.

AVs are indicated for the treatment of allergic rhinitis (AR). AR is a nasal inflammatory disease that affects more than 400 million people worldwide [201]. According to the Gell and Coombs classification system AR is a Type I hypersensitivity disorder, which is initiated by an immunoglobulin (Ig) E-mediated hypersensitivity to aeroallergens [1]. This kind of immune reaction,

which is mediated by T-helper (Th) type 2 cells, is an inappropriate response against the offending aeroallergen. Seasonal AR (SAR) is caused by allergens found outdoors, such as pollen from trees, grasses or weeds, during respective pollen seasons, while perennial AR is caused by allergens found persistently indoors on house dust mites or their feces, moulds or animal danders. AR is characterized by nasal symptoms of sneezing, rhinorrhea, itching and congestion but can also include ocular symptoms (conjunctivitis). Although AR is not usually a severe disease, it affects day-to-day living, school performance and work productivity. Indeed, the direct and indirect socioeconomic costs are substantial [2] with estimates in the USA reaching US\$1.2–7 billion in indirect costs [201]. Furthermore, it is now recognized that these bothersome but relatively minor symptoms may, if left unchecked, progress in an 'allergic march' to the more serious, potentially life-threatening, condition of asthma [3]. It has been demonstrated that children with AR are more likely to be diagnosed with asthma later in life [4]. Recent follow-up studies indicate that the symptoms of patients treated with AV remain reduced and they use

less medication up to 12 years after treatment [5]. These studies also indicate that those children who receive AV are up to 50% less likely to develop asthma.

It is well established that the prevalence of AR is increasing at epidemic proportions, particularly in the westernized world, with the WHO estimating that by 2010, 40% will suffer from some form of allergic disease [201]. The causes of AR are probably multifactorial, including an underlying genetic predisposition for an atopic phenotype. It has been suggested that the increase in allergic disease in the western world is due to inappropriate exposure to environmental factors that are important in shaping our immunological response to our natural world. The hygiene hypothesis, for example, purports that exposure to Gram-negative bacteria, as one would find on a farm or in healthy gut flora, is reduced owing to increased time spent in artificial, sterile urban environments and the overuse of antibiotics, respectively [6]. In addition, exposure to indoor allergens such as dust mite allergens or outdoor air pollutants such as ozone and diesel particulates are increased [7].

Allergy vaccination is a form of immunotherapy employing gradually increasing quantities of specific allergen, which will desensitize or reduce symptoms to that allergen upon subsequent exposure. Over the many years of its use, allergy vaccination has been recognized as an efficacious treatment strategy for patients suffering from AR and is indicated for those patients with severe seasonal rhinitis who are poor responders to treatment with conventional drug therapy. However, there are varying national views on the appropriateness of this treatment. Meta-analyses by Ross, Nelson and Finegold demonstrated the efficacy of immunotherapy in symptom control but also in reduction of medication use in allergic rhinitis [8]. Importantly, the clinical benefits of immunotherapy have been shown to persist for at least 3 years after treatment discontinuation [8]. In a rigorous meta-analysis, Abramson, Puy and Weiner reviewed 75 randomized controlled trials and demonstrated that AV therapy reduced allergic asthma symptoms and the use of medication, as well as improved bronchial hyperreactivity [9].

Only now are the mechanisms of allergy vaccination being elucidated and knowledge of these mechanisms is continuing to evolve. One proposed mechanism for AVs is the normalization of the Th1 to Th2 balance. Evidence from studies of cytokine levels indicates that AV promotes a shift from a Th2-like to a more Th1-like population of allergen-specific T cells, where Th2 cells are associated with elevated interleukin (IL)-4 and -5 and Th1 cells are associated with elevated levels of interferon (IFN)- γ . A downregulation in the production of allergen-specific IgE, an elevation in the IgG response, particularly IgG₄, and a reduction in the late phase inflammatory response associated with this shift. Another mechanism of action for AVs is through the development of immunological tolerance induced by IL-10 produced by regulatory T (T_{reg}) cells [10,11]. Studies have demonstrated that CD4⁺, CD25⁺ allergen-specific T_{reg} cells are induced and can downregulate the Th2, and eventually the Th1, responses. The cytokines IL-10 and transforming growth factor- β from T_{reg} cells are associated with the production of

allergen-specific IgG₄ and IgA antibodies, respectively. These noninflammatory, so-called blocking antibodies, may act by preventing the interaction between allergen and mast cell-bound IgE by various mechanisms.

In North America, AV regimens typically comprise an open-ended injection schedule of weekly doses of an aqueous solution containing target allergen(s) that gradually increase to an optimal dose (usually greater than 20 injections per year) [12]. Guidelines that include practice parameters have been put out at the national and international levels [12–15]. It is apparent from these guidelines that there is considerable variability in the formulation of vaccine and standardization practices. In North America, both standardized and unstandardized allergen extracts are purchased. As many as ten or more extracts are mixed by the allergist in their clinic as per defined dilution schedules in aqueous formulations according to the sensitivity of each patient. In Europe there is a different approach: AVs are purchased preformulated from the manufacturer in graded treatment sets customized for each patient or presented as standardized, properly licensed products, generally adsorbed to a depot, such as alum or L-tyrosine. AVs are made according to the standardization requirements of European or National Guidelines and the production process and all facilities are monitored routinely by government inspection agencies. In many cases, allergens are made available on a named patient basis [16].

Pollinex Quattro

PQ is an AV for the treatment of seasonal allergies manufactured by the UK based company, Allergy Therapeutics plc. PQ is currently produced to treat allergies to grass pollen (12 grasses and rye), tree pollen (birch or birch, hazel, and alder), olive or 'weed' pollen (e.g., ragweed, *Parietaria* spp., plantain, mugwort, *Chenopodium* spp.). Unlike previous AVs, PQ only requires four preseasonal injections to effectively treat seasonal allergies. This improved efficacy is due to its unique formulation which combines three immunochemical innovations, which include chemically modified allergen(s) or allergoids adsorbed onto a natural amino acid, L-tyrosine depot, and including the adjuvant monophosphoryl lipid A (MPL®).

Dosage & administration

PQ is designed as a four-injection regimen that can be administered any time prior to the relevant pollen season each year. This AV regimen should be administered annually for at least 3 consecutive years. The 3-year minimum yearly administration recommendation is based on a study of grass-pollen allergy vaccination, which has demonstrated persistent long-term effects after 3–4 years of treatment [17]. As discussed below, evidence from a large postmarketing study on PQ demonstrated a similar trend toward improvement in symptoms and medication use in the second and third years of vaccination. The vaccination schedule used in the clinical trials of PQ in patients with seasonal allergic rhinitis to grass or tree pollen consists of three 1-ml injections, at weekly intervals, of increasing strength

vaccine (300, 800 and 2000 Standardized Units [SU]/ml) followed by a fourth, full-strength dose (2000 SU) after 1–4 weeks. Injections are given subcutaneously in the upper arm.

The Pollinex family of AVs was first launched in 1972 in the UK by Beecham Group Ltd. and included grass allergoids on a tyrosine depot (Pollinex). This was followed by Pollinex-R (with similar formulation but including ragweed allergoid) made available to the Canadian market in 1975. Subsequently, similar formulations for tree pollens and other pollens endemic to the German and Southern European markets, respectively, were made available. Smith Kline Beecham (SKB) (London, UK) obtained the rights to use the novel adjuvant MPL in the development of AVs from Ribi ImmunoChem (MT, USA) and in 1999 the present formulation of Pollinex Quattro, which comprised a modified allergen tyrosine absorbate (MATA) with MPL, was launched in Germany by Allergy Therapeutics®. Allergy Therapeutics purchased the Bencard vaccine division from SKB in 1998. Allergy Therapeutics has good patent cover for the PQ formulation [101].

PQ has been available on a named-patient basis in Austria, Germany, Italy, Portugal, Spain and the UK, with over 143,000 PQ treatment sets already sold in Europe, providing a considerable amount of postmarketing surveillance data to monitor product safety and efficacy. Unlike some other AVs, PQ is available as a single allergoid or as an allergoid mixture in standardized doses. On the basis of this experience, Allergy Therapeutics has launched an ambitious product development program for PQ worldwide in all major jurisdictions including Canada, USA and Europe to seek product registration.

Pollinex Quattro formulation: pharmacodynamic & pharmacokinetic implications

Modified allergen extract, the allergoid

The allergen extract used in PQ is chemically modified with glutaraldehyde to yield an allergoid [18]. The allergoid has reduced reactivity with IgE (i.e., reduced allergenicity) whilst maintaining immunogenicity, thus retaining efficacy of the vaccine, as well as reducing potential local or systemic reactions. The addition of the bifunctional reagent glutaraldehyde to the allergen extract causes either internal or external cross-linking of proteins through primary amine groups present on the N-terminus and the amino acid, lysine. Injection of glutaraldehyde modified allergen extract, as opposed to unmodified extracts, into animal models results in less induction of IgE antibodies but a maintained ability to bring about the production of allergen-specific IgG [19]. The PQ treatment set for grass allergoids are provided in increasing strengths for 3 weekly injections at 300, 800 and 2000 SU/0.5 ml followed by another injection (1–4 weeks later) at the highest dose [20]. The cumulative dose of the injection course is 60 µg of group one grass-pollen allergoid. The comparable therapeutic treatment sets for PQ for tree-pollen allergoids (alder, birch, hazel) contain 300, 800, 2000 and 2000 SU/0.5 ml and for ragweed 300, 700, 2000 and 6000 SU/0.5 ml.

L-tyrosine depot

Depots have been used historically in order to reduce local and systemic adverse reactions by reducing the immediate bioavailability of the injected allergen. In addition, depots have been used to enhance the immune response to the adsorbed allergen extract. PQ uses the naturally occurring amino acid L-tyrosine as a depot upon which modified allergens are adsorbed. L-tyrosine is normally physiologically present in blood at 0.5 mg/kg (for a 60-kg person) and is provided at a level of 0.3 mg/kg per injection in PQ formulations, a 2% w/v concentration in PQ. The L-tyrosine depot is weakly soluble at neutral pH and allows both the effective adsorption of allergen and its slow dissolution following subcutaneous injection, with a 48-h half-life [21]. In addition, it was demonstrated by Baldrick and colleagues in their review of animal and human studies on the L-tyrosine depot performed before 2002, that L-tyrosine independently acts as an adjuvant by enhancing IgG antibody induction with little additional stimulatory effect on IgE antibody level [21].

MPL, the adjuvant

Further improvements in PQ efficacy are conferred by the additional depot adsorption of the novel adjuvant 3-deacylated MPL, at 50 µg/ml. MPL is derived from detoxified lipopolysaccharide (LPS) originating from the Gram-negative bacterium *Salmonella minnesota* R595. Studies in both animals and humans have demonstrated that MPL demonstrates a suitably nontoxic profile but retains the immunostimulatory activity of the parent LPS molecule [22]. MPL is thought to work as a Th1-inducing adjuvant by being recognized primarily by the Toll-like receptor 4 for pathogen-associated molecular pattern, which are present in LPS and its derivative MPL [23]. This initiates an intracellular signaling cascade that leads to the development of antigen presenting cells into type 1 dendritic cells which drive the Th1 response. Importantly, these dendritic cells must encounter both the antigen and the MPL-pathogen-associated molecular pattern signal to mature and migrate to a draining lymph node where they become active and therefore the MPL stimulus alone is not capable of mounting this response. AVs containing MPL are associated with an antibody switch away from IgE to allergen-specific IgG₁ and IgG₄ in humans [24]. Recent *in vitro* work on human peripheral blood mononuclear cells obtained from patients with grass-pollen allergy showed that the use of MPL with grass-pollen extract results in a promotion of Th1 responses in an IL-12 and monocyte-dependent fashion [25]. Furthermore, experimental work in animals has indicated that the depot-tyrosine and MPL can work synergistically with antigens in producing a shift from Th2 to Th1 response [26].

GlaxoSmithKline has incorporated the MPL adjuvant in a number of vaccines, which are currently in various drug development phases, including those for hepatitis (Fendrix®, registered in 2005), herpes simplex virus 1, 2 (Simplirix®), malaria (Mosquirix®) and human papilloma virus/cervical cancer (Cervarix®) to name but a few.

Clinical efficacy

The clinical efficacy of PQ has been assessed in humans in three studies and a large postmarketing surveillance study (described below). In these studies, clinical efficacy was assessed by measuring the immunological response as indicated by levels of allergen-specific immunoglobulins or cytokines and/or the allergenic response as indicated by any altered sensitivity to the skin-prick test, as well as examination of the therapeutic efficacy as derived from patient recorded symptoms and medication use. Notably, the latter outcome was usually the primary efficacy variable in most studies.

There have been two published randomized, double-blind, placebo-controlled, multicenter studies in adults that have assessed both therapeutic efficacy and limited immune responses. One study evaluated PQ containing grass-pollen allergoids [27] and the other evaluated PQ with tree-pollen allergoids [28]. A third study was an open, nonplacebo-controlled, multicenter study performed in children and adolescents (aged between 6 and 17 years) using PQ for both grass and tree pollens [29]. In all cases, patients had seasonal allergic rhinitis and/or allergic asthma as confirmed with a positive skin-prick test, as well as a positive radioallergosorbent test (RAST) to the culpable pollen. Patients were treated with four injections of vaccine with courses ending at least 2 weeks prior to the start of the target pollen season. Patients recorded their symptoms and use of medication for 1 month during the target pollen season. In all cases, patients were given three PQ injections containing three increasing doses of allergoid (300, 800 and 2000 SU) at weekly intervals and a further top dose (2000 SU) between 1 and 4 weeks interval. Each injection was 1.0 ml and contained 50 µg MPL with L-tyrosine (2.0% w/v). In the two placebo-controlled trials, placebo injections consisted of L-tyrosine (2.0% w/v) in an excipient solution alone.

In both clinical trials in adults, the primary efficacy parameter was the median Combined Symptom and Medication use Score (CSMS) obtained from diary reports which were completed daily for 4 weeks [27,28]. This consisted of recording whether the symptoms from the eyes, nose and lungs that day were scored as none (0), mild (1), moderate (2) or severe (3). The rescue medications provided were those used typically to control seasonal allergic rhinoconjunctivitis and included local and systemic antihistamines, bronchodilators, topical steroids and cromoglycates; with some medications provided in combination. Systemic corticosteroids and long-acting antihistamines were excluded. The medication scoring system allocated one point per organ treated. Other parameters compared were allergenicity as assessed by skin-prick sensitivity and immunogenicity as assessed by pollen-specific immunoglobulins IgG and/or IgE monitored at baseline, middle and end study timepoints. In the open study in adolescents and children, the primary efficacy parameters were patient-rated global scores in which symptoms were rated separately on a 12-point scale and use of medication on a four-point scale [29]. Allergenicity and immunogenicity were also investigated as described above in adult trials.

In the PQ grass-pollen study, the median daily CSMS was significantly lower in patients receiving the AV ($n = 74$) compared with those receiving placebo ($n = 50$; $p = 0.013$) [27]. Interestingly, when analyzed separately, symptom scores alone remained significantly lower in the treatment group compared with the placebo group ($p = 0.003$) but use of medication between the two groups, although reduced, was not significantly different. Skin-prick sensitivity (as indicated by wheal area in mm²) was significantly reduced from that observed at baseline (before treatment) in the active treatment group compared with the placebo treated group ($p = 0.04$).

Serum levels of grass pollen-specific IgG were significantly higher in the active treatment group compared with the placebo group ($p < 0.01$) at two study time points, 2 weeks after treatment had begun and at the end of the grass-pollen season but not at baseline before treatment had commenced. This rise in IgG antibody was noted, by the authors, to be rapid compared with other studies of tyrosine allergoids [27]. Concomitantly, there was no rise in specific IgE resulting from the therapy but also the rise due to seasonal exposure to pollen seen in the placebo group was prevented by treatment ($p = 0.002$). The IgG/IgE ratio was also significantly greater for the active AV treatment group versus the placebo treatment group at all time points measured after treatment.

In the PQ tree-pollen study, the median CSMS score in patients treated with active tree pollen AV ($n = 39$) was significantly lower than that in the placebo treated group ($n = 19$) with the median CSMS being reduced to 3.0 ± 7.6 in the active treatment group compared with 7.2 ± 9.0 for the placebo group ($p = 0.028$) [28]. The skin-prick sensitivity was significantly reduced by approximately half after active treatment but not after placebo treatment ($p < 0.01$). Similar to that observed for grass-pollen study, the tree pollen-specific IgG was significantly higher in the AV treated group with a 40% increase in IgG after 2 weeks of treatment while the IgG levels remained constant in the placebo group ($p < 0.01$). During pollen season, IgE increased significantly in the placebo group ($p < 0.01$) but was significantly reduced in the treatment group ($p = 0.04$).

In the unblinded PQ study on children and adolescents, the global symptom score for the active AV treatment group for either grass-pollen allergic patients ($n = 23$) or tree-pollen allergic patients ($n = 63$) was significantly improved after the pollen season compared with baseline scores ($p < 0.01$) [29]. Similarly, medication use was reduced significantly for both treatment groups after the pollen season compared with their baseline levels ($p < 0.01$). Skin-prick test sensitivity was also significantly reduced ($p < 0.05$) compared with baseline levels in both groups as early as 2 weeks after therapy, and remained significant until the end of the pollen season. Pollen-specific IgE (for grasses or trees) levels was stated in the report to increase slightly in both groups, however, data were not shown. Pollen-specific IgG for each respective group was significantly increased over their baseline levels both at 2 weeks after therapy

and after the pollen season had ended (in all cases $p < 0.05$). On the whole, these findings are consistent with data from placebo-controlled, double-blind studies in adult patients. More studies are required to determine how PQ, or indeed any SIT, may modify allergic disease in children.

Four small clinical studies ($n \leq 21$) have been performed in which the primary efficacy parameters measured were solely immunological indicators, such as immunoglobulins and/or cytokines [24,30–32]. These indicators were measured at various time points during and after PQ vaccination and these results are summarized in TABLE 1.

Investigational trials

Allergy Therapeutics is currently conducting investigational studies for the registration of PQ in standardized treatment sets in Canada and the USA. Specifically, Allergy Therapeutics has opened three investigational new drug applications with the US FDA covering PQ vaccines against seasonal allergic rhinoconjunctivitis caused by grass, ragweed and tree pollens. In Canada, eight clinical trial authorizations have been granted by

Health Canada, covering all three pollen formulations of PQ. These open authorizations to conduct trials using American and Canadian patients cover a number of late Phase II/Phase III studies, ranging from small skin test studies to a large Phase IIb/III double-blind, placebo-controlled efficacy study.

Phase I

More recently, two small Phase I studies have evaluated the local response by measuring skin-prick sensitivity of PQ for tree and ragweed pollen allergoids using skin-prick testing [33]. The findings of these studies and those discussed above have been consistent with early reports [34], which indicate that glutaraldehyde modification of allergens, as well as their adsorption onto the L-tyrosine depot, reduce allergenicity of PQ [27–29]. In a single-blind study with 12 patients allergic to ragweed pollen, patients had skin-prick tests with the following test products: native ragweed allergen (1.0909% w/v + 6 serial 1:3 dilutions), ragweed allergoid (1.0909% w/v), ragweed allergoid tyrosine adsorbed (6000 SU/0.5 ml), ragweed allergoid tyrosine adsorbed plus MPL

Table 1. Immunological changes induced by Pollinex® Quattro.

Author(s)	Subjects (n)	Mean years	Allergoid tested	Study design	Findings: immune responses	Ref.
Mothes <i>et al.</i> (2003)	n = 20 9 Placebo + 11 Active treatments	NA	13 grass pollen allergoids: rye, meadow foxtail, dogtail grass, orchard grass, rye grass, kentucky bluegrass, vernal grass, fescue meadow, bentgrass, timothy grass, brome grass, oat grass and velvet grass	Unblinded, placebo-controlled	Increased IgG ₁ and/or IgG ₄ responses both to natural Timothy grass extract and to recombinant Timothy grass allergen rPH1 p5 No change in IgE production during the grass pollen season that was mainly directed against rPhl p5 allergen. Increased IgM response to Timothy grass allergens observed in a subset of actively treated patients Decreased allergen-dependent basophil histamine release in sera containing therapy-induced IgG antibodies	[24]
Stuck BA <i>et al.</i> (2004)	n = 14 5 Placebo + 9 Active treatments	39.3 ± 13.7	Birch pollen allergoid	Randomized, prospective, double-blind, placebo-controlled	Increased release of the cytokine IFN- γ (IS & PS, $p < 0.001$). Decreased IL-4 (IS, $p < 0.01$; PS, $p < 0.05$) and IL-5 (IS, $p < 0.01$; PS, $p < 0.001$) from T cells stimulated by allergen challenge in an <i>in vitro</i> assay	[30]
Rover AC <i>et al.</i> (2002)	n = 12 4 Placebo + 8 Active treatments	31.5 ± 11.4	Hazel, Alder and Birch pollen allergoids	Unblinded, placebo-controlled	No significant differences were discerned in antibody profiles for pollen-specific IgE or IgG Decreased CD23, CD54 and HLA-DR-II expression on patients' blood B cells	[31]
von Baehr <i>et al.</i> (2005)	n = 35 14 Untreated controls + 21 Active treatments	NA	Grass and/or Mugwort pollen allergoids	Unblinded, controls grass and/or mugwort allergic patients	LTT stimulation occurred in 17/20 patients both at mid- and end-treatment time points compared with pretreatment levels. Five months after treatment, LTT stimulation indices had returned to baseline levels	[32]

HLA: Human leukocyte antigen; IFN: Interferon; Ig: Immunoglobulin; IL: Interleukin; IS: Intraseasonal; LTT: Lymphocyte transformation test; NA: Not available; PS: Postseasonal.

(6000 SU/0.5 ml) positive control histamine solution (0.1%), and negative control glycerinated extraction medium. Skin-prick tests for each test product were duplicated on each forearm. Residual allergenicity of test products was determined by the difference in the area (mm^2) of the wheal response for each test product and glycerinated extraction medium. In each patient the seven wheal areas from the native allergen were plotted against concentration to produce a concentration–response plot. The wheal areas from the three allergoid products were compared with that plot and the corresponding native allergen concentrations estimated using linear interpolation. The calculated median activity of the aqueous allergoid (1.0909% w/v) was found to be equivalent to approximately 1/47th of the corresponding aqueous native allergen. The calculated median activity of PQ ragweed was approximately 1/225th of aqueous native allergen. No drug-related adverse events and no late-phase allergic reactions of more than 10 cm were observed following exposure to any allergens tested. These results indicate the allergoid contained in PQ ragweed elicited only a fraction of the allergenicity of its progenitor product, at the same pollen concentration.

Phase II

A total of 11 late-stage Phase II studies have been conducted in North America involving 700 patients since 2005. Under the grass allergy program, four studies have been completed, one named G203, was discussed in a press release in March 2006 [202] and a recently published abstract [35]. G203 was a double-blind, multicenter Phase II study to evaluate the immunogenicity and tolerability of different doses of PQ for grass. This trial involved 74 patients with a history of moderate-to-severe seasonal rhinoconjunctivitis, a positive skin-prick test and a positive RAST to grass and rye allergen received 4 weekly subcutaneous injections with one of the three study test products (low dose, intermediate dose or therapeutic regimen or placebo). Immunogenicity was assessed by the serum concentration of grass-specific immunoglobulins (IgG, IgG₁, IgG₄ and IgE to timothy, june and rye) compared between the PQ grass treatment arms and placebo.

Analyses showed that the low, intermediate and therapeutic regimens treatment groups all had increased immunoglobulin levels over time relative to baseline levels [35]. These increases appeared to be dose-dependent with the therapeutic dose regimen yielding the highest increases over baseline more often. Primary analyses of Timothy grass-specific immunoglobulins showed significant changes over baseline occurred most often with the therapeutic dose regimen by visit six (visit six occurred 2 weeks after the last of the 4 weekly AV injections), with net changes over placebo in specific IgG, IgG₁, IgG₄ of 59.9, 87.8 and 105.9% ($p = 0.042, 0.005$ and 0.009), respectively. Similar trends in the change in IgG, IgG₁ and IgG₄ immunoglobulins specific to rye and june grass were observed. There were no serious adverse experiences or severe systemic reactions reported during the study. Only minor adverse experiences were observed and these included injection site pain, itching or swelling.

Most recently, a study has been conducted to evaluate the clinical efficacy and safety of PQ for ragweed allergy. R204 is a pivotal Phase III and IIb study from the ragweed program necessary for the registration of PQ in Canada and the USA, respectively. The preliminary findings of this trial were discussed recently in a press release in April 2006 [203] and in an abstract [36]. The study was a randomized, double-blind, placebo controlled, Phase IIb/III study to evaluate the clinical efficacy and safety of PQ-ragweed conducted in an Environmental Exposure Chamber (EEC) operated by Allied Research International (CA, USA). The EEC provides an ideal setting to perform aeroallergen studies since the duration of allergen exposure can be tightly controlled and reproduced. The use of the EEC for clinical trials to study allergic rhinitis has been encouraged by the FDA and its European counterpart, the European Agency for the Evaluation of Medicinal Products, owing to reduced study variability and superior sensitivity to discern drug efficacy parameters such as onset of action, dose-response and optimal dosing. In this setting, R204 was conducted and involved 177 patients with a history of moderate-to-severe seasonal rhinoconjunctivitis, a positive skin-prick test and a positive RAST to ragweed allergen.

An innovative study design was used in which patients had a baseline, pretreatment exposure to ragweed pollen in the EEC for 3 h during 4 consecutive days and recorded nasal and non-nasal symptoms every 30 min. These patients then received four weekly subcutaneous injections with either PQ ragweed ($n = 95$) or placebo ($n = 93$). After a period of approximately 3 weeks to allow for the immune response to develop, patients had a second, post treatment, series of ragweed exposures in the EEC.

The primary efficacy parameter assessed was the change from baseline in the post treatment Total Symptom Scores (TSS) in PQ-ragweed-group compared with the placebo-treated group. TSS is a combination of nasal (rhinorrhea, congestion, sneezing and itchiness) and non-nasal (itchy/gritty eyes, tearing/watery eyes, red/burning eyes, ear/palate itching) allergy symptoms. Importantly, all scores are instantaneous (how patients felt at that moment) as opposed to reflective scores (patients remember how they felt since the last measurement). A four-unit scale was used for patient evaluations of the above symptoms with 0 = none, 1 = mild, 2 = moderate, 3 = severe with a maximum possible score of 24. Immunogenicity was assessed based on changes in immunoglobulin levels, ragweed-specific IgG from baseline in EEC pre-treatment (visit five) to post treatment (visit 11) and to end of the study (visit 14). Another secondary objective was to evaluate the impact of PQ ragweed versus placebo on quality of life in patients with SAR using a Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) recently developed and validated by Allied Research International specifically for use in the EEC [37].

The results demonstrated that the TSS at baseline for all treatment groups was comparable. However, after the four injection course of PQ ragweed, the TSS had fallen to 9.1 from a baseline value of 15.7, a significant decrease in

symptoms ($p < 0.01$) compared with control. This corresponds to a change in symptom severity from 'moderate' to 'mild'. The onset of the reduction in symptoms was visit 11. This change in symptoms was supported by a marked increase in ragweed-specific IgG in which there was a near 100-fold larger increase in IgG with active treatment compared with placebo ($p < 0.001$). Analyses of the EEC-specific RQLQ indicators showed that patients treated with PQ showed a greater improvement in the practical problems domain of the RQLQ than the placebo group ($p < 0.0004$) and for overall global assessment compared with placebo ($p < 0.028$).

This study is an important component of the global registration strategy. R204 will form the basis for completion of Phase II and III trials in Canada and the USA, respectively. Final development studies will be underway by 2007 following recent discussions with the FDA during an end of Phase II meeting [PERS. COMM. FROM ALLERGY THERAPEUTIC]. A follow-up study is currently underway to investigate whether the beneficial therapeutic efficacy and immunogenicity are retained from R204.

Postmarketing surveillance

A large postmarketing surveillance (PMS) study was conducted to retrospectively examine the efficacy and tolerability of PQ in a selection of formulations for a number of aeroallergens including grasses plus rye, three trees (birch/alder/hazel), mugwort, plantain, fat hen, parietaria, olive and ragweed according to individual prescriptions. The main formulations administered in this PMS study were grasses/rye (37.6%) and three tree (31.4%). This multicenter study was conducted in doctors' offices and hospitals in Germany over 3 years, from September 1999 to August 2002, in 963 centers and included a total of 3114 patients, with 2235 patients receiving treatment for 1 year, 555 patients receiving treatment for 2 years and 324 patients receiving treatment for 3 years. A total of 422 patients (over the last 2 years of the study) were children or adolescents between 6–17 years of age. Patients who had seasonal AR/rhinoconjunctivitis and/or allergic asthma to one or more of the allergens tested (as outlined above) were included. Combinations of allergens were provided for a maximum of four allergoids. Physicians who participated in the study belonged to the following specialties: internal medicine, ear, nose and throat, pediatric, dermatology and general practitioner. Two reports have been published on this PMS, one summarizing the results after 1 year [38] and one in abstract form on the results after all three years [39]. In both cases the efficacy was estimated by medication use (patient reported) and

symptoms (physician reported global assessment of efficacy) in comparison with those recorded for the previous pollination season(s). Tolerability was assessed by the frequency and intensity of local and systemic adverse reactions.

As shown in FIGURES 1 and 2, for those patients who were in the study for all 3 years ($n = 324$), after 1 year, 88.3% of patients had improved symptoms and their use of anti-allergic medication during pollen season had decreased such that 55.6% took medications only 'occasionally' compared with 16% before therapy [28,39]. Furthermore, 18.2% of patients said that they did not require any medication during pollen season after therapy compared with only 2.5% prior to therapy. The efficacy of PQ improved over the course of the PMS [39]. This was assessed by studying 324 patients who were in the PMS for all 3 years. Here, physicians reported that 93.5% of patients in each of the subsequent 2 years had improved symptoms (FIGURE 1). As shown in FIGURE 2, medication use had also declined with 6.2% of patients reporting that they still required frequent anti-allergic medications after 3 years of treatment with PQ compared with 35.2% of patients before treatment. Also, the percentage of patients who only required 'occasional' or 'no' treatments increased to 52.2 and 32.1%, compared with 16 and 2.5% before treatment with PQ, respectively [39].

Tolerability was assessed by the physician by recording the patient's response to the treatment as 'very good', 'good', 'less good' or 'bad'. For those patients with 3 years of treatment, the tolerability of PQ was rated as 'good' or 'very good' in the majority of cases. When all 3114 patients in the PMS were examined, it was found that 93.4% of adults (2692 patients) or 93% (422) of children/adolescents patients found the treatment to be 'very good'. The frequency, severity and outcome of any local or systemic adverse events were documented during treatment. Over the course of 3 years, 21,428 injections were administered. Of the patients who

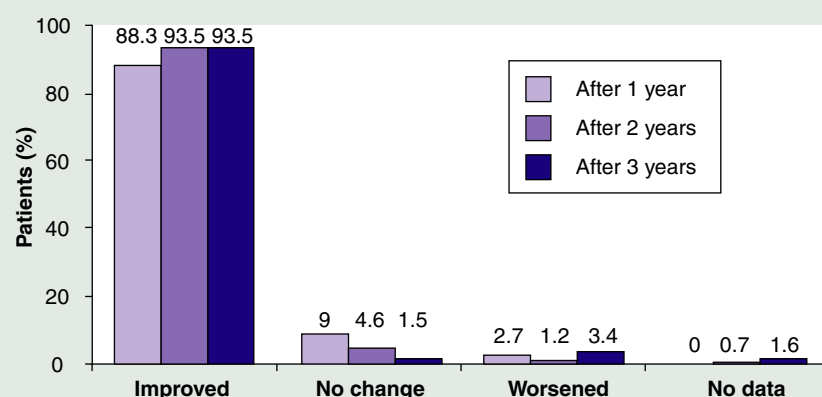


Figure 1. The therapeutic success of treatment with Pollinex® Quattro (PQ) for grass, tree and weed pollen allergens.

The graph indicates that there was 88.3% symptom improvement after 1 year of PQ vaccination. 93.5% of patients were reported by physicians to have improvement in symptoms in the second and third years ($p = 0.004$).

Reproduced with permission from [39].

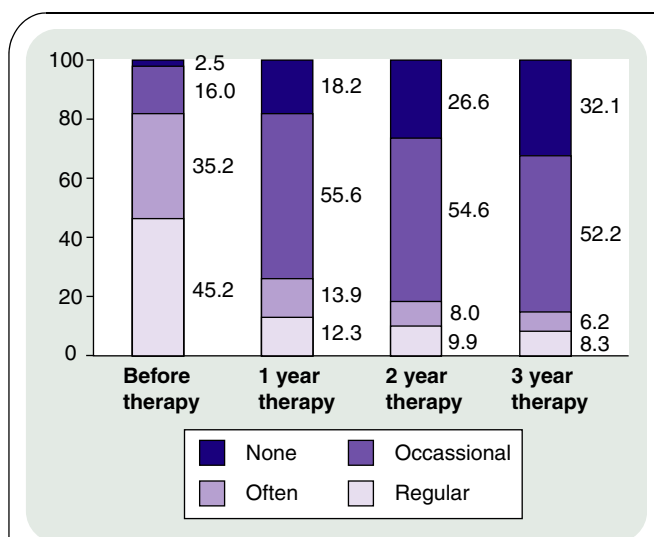


Figure 2. Medication use after vaccination with Pollinex® Quattro for grass, tree and weed pollen allergens.

The graph indicates that the use of anti-allergic medication declined significantly after 1 year of therapy ($p = 0.0001$). Further reductions in medication use occurred after 2 and 3 years of therapy ($p = 0.0004$, $p = 0.04$). The results show a marked reduction in the 'regular' and 'often' use of anti-allergic medication. Notably, before therapy, 2.5% of patients used no anti-allergic medication compared with 32.1% of patients reporting they did not require anti-allergic medication.

Adapted with permission from [39].

participated over the 3 years, 6.3% of injections were followed by a local reaction. Most of the local reactions reported were redness and swelling of 5–10 cm diameter. Pain and itching at the injection site were also recorded. Notably, local reactions declined with time, with local reaction reduced to 4.9 and 4.3% in the second and third years, respectively. Systemic reaction occurred after 0.7% of injections. Systemic reactions also declined over time with 0.25 and 0.34% in the second and third years, respectively. These reactions were characterized most often as mild rhinitis. Breathing problems were reported in 13 cases although the majority were mild-to-moderate. Generalized urticaria was reported in three cases and only two of these cases were definitively related to therapy. One of these patients received antihistamine treatment, the second underwent a dose adjustment and both recovered completely. According to the European Directive, none of the systemic events were classified as serious and no anaphylactic reactions occurred after any injections of PQ at any time point in this 3-year study [40].

Tolerability & safety

The WHO indicates that severe adverse reactions to AVs are indeed rare but anaphylactic reactions to subcutaneous immunotherapy do occur and that no single event is trivial [13]. In fact, the nature of allergy vaccination is such that the administration of an allergen to which a patient is hypersensitive contains the potential for adverse reactions. This, coupled with the long dosing schedules typical of older

AV regimens, has made allergy vaccination an unattractive treatment option. In general, the improved quality control of the standardized extracts now used has also further reduced the likelihood of any severe reaction and recently published practice parameters have provided guidance such that AVs are now used appropriately by trained physicians, which has led to a further reduction in serious reactions [14].

PQ is standardized according to regulatory requirements and an overall standardization process has been developed which includes excipient control by standard quality control assays [41]. Allergoids, the active ingredients, are monitored to be kept within specification during all stages of manufacture by validated allergen assays. With PQ, the allergoid in the final product is assayed as an antigen by specific IgG using an assay system with a europium label [42]. Importantly, an assay to monitor the MPL component both before and after incorporation into the tyrosine adsorbate using high pressure liquid chromatography technologies has been developed [41]. These well defined standardization procedures have resulted in inter-batch consistency with respect to all of the PQ components, which reduces the likelihood of adverse reactions due to product inconsistencies.

PQ combines three immunochemical innovations which act synergistically to not only improve the therapeutic efficacy but also the vaccine safety. Chemical modification of the native allergen with glutaraldehyde modifies allergens such that their reactivity with IgE is greatly reduced thereby reducing the potential for local adverse reactions and improving safety. Adsorption of the allergoid onto a natural L-tyrosine depot results in the slow release of allergoid, which also acts to reduce the immediate bioavailability of the allergoid reducing the potential for local and systemic adverse reactions. Similarly, the use of the MPL adjuvant reduces the amount of allergoid required to reach peak immunological responses required for allergen tolerance development.

Since its introduction in 1999, over 500,000 injections of PQ have been provided to more than 70,000 patients worldwide to treat allergic rhinitis. As indicated above, the 3-year PMS study indicated that there were no instances of anaphylaxis and that, in fact, the incidences of both local and systemic adverse events decreased over time [39]. In the published studies reviewed, the grass and tree pollen formulations were well tolerated with most adverse events being limited to local inflammatory and immunostimulatory reactions at the injection site [27–29]. These results were consistent with preclinical toxicology and tolerability studies in animals which also reported local injection-site reactions as the most common adverse event [43].

In the PQ-grass study, local injection-site redness and swelling, as well as itching, occurred more often in the active treatment group compared with placebo [27]. In the PQ-tree study, the incidence of redness and swelling was also higher in the active treatment group compared with placebo, with the incidence of 5–10 cm diameter wheal being 19.2% in the active treatment group compared with 5.5% in the placebo group [28]. In pediatric patients, the incidence of redness and swelling for either grass or

tree pollen vaccines were not significantly different, however, itching was reported to occur more often in patients treated with the tree pollen vaccine [29]. Systemic adverse events to grass or tree pollen vaccines occurred with similar incidences in active treatment and placebo groups and consisted mostly of rhinoconjunctivitis [27,28]. Reported systemic adverse events included itching, nausea, headache, arm or hand joint pain, migraine, hot flushes, hypotension, chills, breathing difficulties and tachycardia but these symptoms occurred in a very low percentage of patients.

Conclusion

The studies published to date indicate that PQ is a highly effective preseasonal immunotherapy vaccine for the treatment of SAR and rhinoconjunctivitis. Importantly, improvements in symptoms are conferred after an ultra short-course schedule of only four pre-seasonal injections over as little as 3 weeks. This improved efficacy with rapid immunotherapy regimes is the result of the combination of chemically modified allergens with a novel adjuvant adsorbed onto a slow-release depot. PQ is the only allergy vaccine to combine all three approaches and to include the adjuvant MPL. Preliminary results from a pivotal study in Canada have indicated that there is significant clinical improvement in symptoms in just 3 weeks after completion of treatment with symptoms improving categorically from moderate to 'mild'. These findings are consistent with previous published studies with PQ for tree and grass pollen allergens. In addition, all studies where immunological indicators were measured demonstrated that the underlying disease phenomenon is also altered with this short treatment such that there is a significant increase in allergen-specific IgG and IgE induction is blunted. To date, clinical trials, as well as the findings from a large postmarketing surveillance study, show that PQ is very well tolerated with a low incidence of local and systemic reactions.

Expert commentary

Although AV has been used for many years and has been shown to be efficacious, most allergic patients are still treated solely with symptomatic drugs. In many cases AV therapy is not recommended even when there is a clear indication. This has been largely owing to safety concerns. AV therapy by the nature of the therapy, which involves injection of solution of proteins to which patients are hypersensitive, holds the potential for adverse reaction either at the site of the injection or systemically with anaphylaxis. Even though severe adverse reactions are rare with AV, they remain a valid and important concern [13]. In addition, long dosing schedules with traditional aqueous allergen extracts has made AV therapy unattractive. PQ has been formulated to address both of these therapeutic concerns by combining chemically modified allergens with an immunostimulatory adjuvant, MPL, to provide a rapid immunotherapy regime that has been shown here to be clinically efficacious and well tolerated with few adverse reactions in placebo-controlled double-blind clinical trials.

Unlike other AVs, PQ was efficacious after an ultra short-course of only four injections applied preseasonally over as few as 3 weeks. This is in contrast to typical aqueous AVs with

allergen extracts with a high number of injections, usually more than 20, required per treatment course. Furthermore, retrospective analyses of PMS indicate PQ therapy may be effective when applied any time during the year (excluding the culpable aeroallergen season). Compressing the number of injections into shorter periods that can be applied in any pre-seasonal time window during the year improves patient compliance and optimizes treatment.

The incorporation of MPL into PQ is largely responsible for the improved efficacy of the product. MPL is a well characterized product but the mechanisms by which it exerts its desensitization effects are complex. MPL does contribute to the enhanced immunogenicity of PQ and importantly has also been shown to act synergistically with the tyrosine depot in producing a Th1 response. PQ is currently the only AV to incorporate MPL.

Clinical studies and the large PMS study have indicated that localized adverse reactions were minimized with PQ. This is probably the result of the chemical modification of the allergen to an allergoid, which acts to reduce reactivity with IgE, in combination with the ability of the L-tyrosine depot to reduce the immediate bioavailability of the injected allergoid. Systemic reactions are also rare with PQ and tend to be mild. This is probably the result of a combination of depot and adjuvant actions to reduce the effective allergoid dosage required to reach peak desensitization.

Taken together, the improvements in patient safety, efficacy and compliance observed in studies on PQ indicate that allergists will convert to treatment of their patients with this AV, particularly in North America where AVs used most often are still aqueous formulations of allergen extracts mixed in the allergists' offices. Allergists are likely to offer such an ultra short-course treatment option as much as their patients are to request it, when they become aware of its availability. PQ availability will be through pharmacy procurement, akin to drug therapies, upon registration. The standardization and provision of PQ in treatment sets will require less physician preparation and treatment time per patient. This will allow physicians to provide therapeutic relief with PQ to more patients more efficiently.

PQ is a seasonal AV that exemplifies the next generation of bioengineered allergy vaccines and combines chemical and immunological innovations leading to improved safety, efficacy and patient compliance. Further improvements in formulation could alter allergoid, adjuvant and/or depot content. For example, glutaraldehyde-modified allergoids could be replaced by hypoallergenic allergen derivatives. Here, allergens are genetically modified such that their IgE antibody combining sites are mutated and they do not react with the IgE antibody. These allergen derivatives retain the ability to react with T cells but are safer [44]. Also, synthetic analogues of MPL may be used which are currently being developed [45].

More recently, alternative modes of delivery of AVs have been explored. Sublingual immunotherapy vaccines (i.e., drops or tablets placed under the tongue) are being introduced. This form of therapy is particularly suitable for children, but the efficacy has generally been lower than with subcutaneous

vaccination. Allergy Therapeutics recently announced its intent to conduct a first human Phase I/II trial with a sublingual immunotherapy formulated with the adjuvant MPL [204]. If successful, this study would show that sublingual vaccines demonstrate improved activity with the addition of MPL and could pave the way for the development of new noninjected AVs with improved efficacy, shorter dosing and fewer local side effects. Such sublingual vaccines would offer patients an alternative to injections and could be administered at home. There are currently no other sublingual vaccines with adjuvant available on the market.

Five-year view

Promising outcomes from investigations support the registration bid for PQ and indicate that PQ may complete Phase III in Canada by 2007 and Phase III studies towards US registration are expected to commence in 2006. Allergy Therapeutics is also currently conducting follow-up studies at yearly intervals to assess the longevity of symptom relief and medication use reduction after treatment with PQ in the previous R204 study.

Developments of PQ formulations for other nonseasonal aero-allergens, such as dust mite and cat allergen, and for the treatment of perennial allergic rhinitis are clear development targets. The combined allergen approaches for limited multiple allergies, such as grass and tree, on the same PQ platform may still be routinely available on a customized basis but may also become licensed products, which would help in the drug payment reimbursement in some countries. The potential exists in such a customized regimen for one treatment set of four injections to treat multiple aeroallergen allergies which would be an extremely convenient treatment strategy and improve patient compliance. A treatment combination of no more than three allergens has been recommended in WHO guidelines [13].

Currently, AV therapy is indicated for patients with severe AR that do not respond to medication. Extensive meta-analyses have demonstrated that allergy vaccination is also effective in the treatment of allergic asthma. The increase in the prevalence of asthma worldwide and the potential for AVs to modify the underlying immune response could result in the expansion of indications for AV treatment to include allergic

Key issues

- Allergic rhinitis has been estimated to affect more than 400 million people worldwide and its prevalence is increasing.
- Although pharmacological therapy improves allergic rhinitis symptoms, allergy vaccines (AVs) are the only current therapies that modify the underlying immunological response to inhalant allergens, providing sustained relief of symptoms over many years and which may even prevent progression to more severe forms of allergy.
- Until now in North America, AVs have been characterized by series of open-ended injection schedules of increasing doses of allergen extract injections using very long courses (usually ~20 injections), which may result in suboptimal treatment due to lack of compliance.
- Pollinex® Quattro (PQ) is a new AV, which is indicated for the treatment of seasonal allergic rhinoconjunctivitis and has been shown to be efficacious after only four injections prior to the relevant pollen season.
- The benefits of PQ are the result of the combination of three immunochemical innovations. First, chemical modification of allergen to allergoids reduces allergenicity while retaining immunogenicity of these. Second, their adsorption onto the slow release L-tyrosine depot reduces the likelihood of an immediate adverse event. Third, the adsorbed immunological adjuvant monophosphoryl lipid A (MPL®) enhances efficacy and allows a short injection regime to give satisfactory results.
- PQ has been shown to be efficacious in a number of published clinical trials to reduce median combined symptom scores and medication use.
- PQ is safe and well tolerated as demonstrated in a number of published clinical trials, as well as in 3-year postmarketing surveillance in which out of 70,000 injections no serious adverse reactions were reported with no incidences of anaphylaxis.
- PQ is now in Phase II in the USA and Phase III in Canada towards PQ ragweed formulation registration.
- Recent promising preliminary results in an investigational trial study (R204) on PQ for ragweed allergen were conducted in an environmental exposure chamber (EEC) indicate that PQ significantly reduces the total symptom score (for both nasal and non-nasal symptoms) with a categorical change of symptoms reported as 'mild' rather than 'moderate'. Additionally, allergen-specific immunoglobulin G titer was 100-fold higher with PQ treatment compared with placebo. Analyses of quality of life using an EEC-specific rhinoconjunctivitis quality-of-life questionnaire developed at Allied Research International Inc. (Ontario, Canada) indicated that problem solving and overall global assessment of quality of life were improved significantly.
- PQ demonstrated improved efficacy owing to immunochemical modifications with a potentially improved patient compliance owing to the ultra short-course treatment schedules.
- PQ product registration may lead to more general acceptance of AV as a treatment option even to be administered by generalists.

asthma. Furthermore, continued demonstration of safety and efficacy could result in an increase in the treatment of pediatric patients with AVs. Currently, more children with allergic rhinitis are treated with AVs in Europe than in North America.

Continued positive results from investigational trials toward registration of PQ will raise the awareness of AV therapy as a real treatment option and will lead to a wider acceptance by all physicians. Such awareness will lead to more referrals to allergists, as well, availability of PQ in standardized treatment sets could result in AV therapy administered by the generalist or other specialist such as dermatologist or pediatrician. Acceptance of modern AV therapy with PQ by the medical community could lead to more governmental acceptance with AVs covered under all state health plans. Recent studies indicate that use of AV therapy is cheaper in the long-term than use of medications, which would provide further economic impetus for its acceptance [48].

Taken together, the clinical improvement in efficacy and tolerability with PQ will result in improved patient compliance and optimize treatment. The ability of PQ to alter the underlying mechanisms of AR potentially in the long-term will result in real symptom relief and reduced anti-allergic medication use for patients, which in the end result translates into meaningful changes in the quality of life of patients.

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