Human Vaccines & Immunotherapeutics

ISSN: 2164-5515 (Print) 2164-554X (Online) Journal homepage: https://www.tandfonline.com/loi/khvi20

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To cite this article: Domingo Barber, Pilar Rico, Carlos Blanco, Montserrat Fernandez-Rivas, Maria Dolores Ibañez & Maria M. Escribese (2019) GRAZAX®: a sublingual immunotherapy vaccine for Hay fever treatment: from concept to commercialization, Human Vaccines & Immunotherapeutics, 15:12, 2887-2895, DOI: 10.1080/21645515.2019.1622976

To link to this article: https://doi.org/10.1080/21645515.2019.1622976

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Accepted author version posted online: 03 Jun 2019.
Published online: 20 Jun 2019.

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HUMAN VACCINES & IMMUNOTHERAPEUTICS
2019, VOL. 15, NO. 12, 2887–2895
https://doi.org/10.1080/21645515.2019.1622976

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PRODUCT REVIEW

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GRAZAX®: a sublingual immunotherapy vaccine for Hay fever treatment: from concept to commercialization

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ABSTRACT

Allergen immunotherapy has been used for more than 100 y, but only recently underlying immunological mechanisms have started to be understood. New Allergy vaccines are now considered to be full pharmaceutical products, that should comply with general as well as specific pharmaceutical legal framework. GRAZAX® is the first global allergy vaccine developed in compliance with the new legal environment and is thus a reference for developing new allergy vaccines. Here, we provide a rationale description of GRAZAX®, providing a sequential description of its pharmaceutical and clinical development. With more than 25 clinical trials, involving more than 8000 patients, including as well three 5-y prospective clinical trials, GRAZAX® is a key product to understand the unique position of allergen-specific immunotherapy as a disease-modifying intervention.

ARTICLE HISTORY
Received 25 March 2019
Revised 24 April 2019
Accepted 15 May 2019

KEYWORDS
Grazax; allergen immunotherapy; allergy vaccine; sublingual immunotherapy; grass allergy

Introduction

Allergen-specific immunotherapy has been used for more than 100 y but only recently allergy vaccination has been included within the pharmaceutical regulatory framework. Until late 80s, only some general guidelines covering mainly particular quality aspects were issued by different regulatory agencies. After the inclusion of allergen immunotherapy (AIT) products within the European Directive of Medicinal Products, the progressive development of specific European Medicines Agency (EMA) guidelines, and European Directorate for the Quality of Medicines (EDQM), European pharmacopoeia monograph, new projects aiming to develop industrially produced AIT products must follow this demanding regulatory framework[1]. This is the case of GRAZAX®. Moreover, when considering a global product as GRAZAX®, the position of non-European regulatory agencies, for example Centre for Biologics Evaluation and Research (CBER)-FDA, had to be taken into account.[2]

During the 1990s, different clinical research groups in Italy started to develop a new way of administering AIT by sublingual route. Several small and investigator-driven studies suggested this new route was effective, with a clear improvement in the safety profile compared to subcutaneous vaccines. The publication of meta-analysis on accumulated evidence on sublingual studies, although with a high heterogeneity, concluded that this route was effective. Sublingual/swallowed administration was recommended and, subsequently, an open debate on the optimal dose was initiated.

Origin and research basis for the design of the product

Despite the sublingual/swallow recommendation, studies performed addressing gastric route alone failed to prove clinical effect. Based on this, the idea came up that a better pharmaceutical formulation, aiming to increase bioavailability of the allergen in the oral mucosa, might improve the effect. The Zydis technology from RP Scherer (currently Catalent) consisted of a freeze-dried tablet pharmaceutical presentation that was successfully used in different drug formulations. This formulation presents a unique bioavailability profile that allows an immediate release of the allergen in the oral mucosa with a maximum local concentration.[3] The incorporation of a *Phleum pratense* allergenic extract onto Zydis platform is the basis of GRAZAX®.

Preclinical and toxicology studies

As previously mentioned, GRAZAX® was based on accumulated experience of sublingual IT in human studies that were basically based on glycerinated aqueous formulations. Besides those studies, the toxicological profile of GRAZAX® was investigated in several *in vitro* and *in vivo* studies, revealing no concerns for its use in human beings. However, there is currently no clinical experience of the use of GRAZAX® in pregnant and lactating women.

Animal models were developed to investigate sublingual mechanism and specifically to prove that fast-dissolving

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orodispersible tablet for sublingual administration was able to reduce allergic symptoms in a time- and dose-dependent manner.[4]

Pharmacokinetics

The allergens in GRAZAX® mainly comprise polypeptides and proteins that are thought to break down to amino acids and small polypeptides in the gastrointestinal tract and in tissues. These allergens are not expected to be absorbed into the vascular system to any significant extent. Consequently, no pharmacokinetic studies are needed to be conducted in animals or in the clinical setting.

Safety testing

GRAZAX® is the first AIT preparation that has been developed prospectively in accordance with Pharmaceutical regulations.

In spite of using an active pharmaceutical ingredient (API) that had been extensively used in other vaccines formulation, in agreement with regulatory bodies of UE and USA, different safety tests were performed following International Council for Harmonisation (ICH) guidelines. Preclinical safety studies included acute and repeated dose toxicity testing, as well as mutagenicity potential (AMES test). No major safety-related observations were found.

Production

Since 1989, directive 89/342 EEC extended the scope of pharmaceutical directive to allergen products. Besides, a specific European Pharmacopoeia monograph on allergen products set the legal basis for allergen product commercialization. Specific note for guidance has been progressively introduced, setting source material as well as final product quality requirements.

Manufacturing layout must follow European Pharmacopeia. An API must be defined and standardized according to regulations. Total biological potency, major allergen content, and appropriate identity test must be implemented. Despite the efforts carried out in the last decades,[5] there is no international reference preparation for *Phleum* individual allergens. To date, only a reference on major allergen for Bet v 1 is implemented.[6] Therefore, a careful internal reference system was implemented. Basic standardization and quality check are performed at the API level. As quality consistency is directly dependent on the quality of source material use for API manufacture, vertical control of all the process is guaranteed, and a specific ALK Group Company, dedicated to source material production of allergens, supply the pollen used for API manufacturing.

API consists of a semi-purified (ultra-filtration) aqueous pollen extract. Extraction conditions are optimized to solubilize proteins under physiological conditions. The extract includes all relevant allergens present in the pollen in native form. No further modification aiming to modify immunological recognition of allergenic component is performed. It must be noticed that immunological recognition of these antigens greatly varies from one patient to another.

API is incorporated into gelatine- and mannitol-containing formulation at the nominal dose deeply frozen and freeze-dried. A detailed description of the GRAZAX® manufacturing and standardization process is described by Römmelmayer et al.[7]

Assays for releasing and characterizing the final product

Specification and release criteria for GRAZAX® are shown in Table 1.

Main test includes physical, chemical, immunochemical, and microbiological criteria.

Indication

GRAZAX therapeutic indication is: Treatment of grass pollen induced rhinitis and conjunctivitis in adult and children (>5-y old) patients with clinically relevant symptoms and diagnosed with a positive skin prick test and/or specific IgE test to grass pollen.

GRAZAX® addresses the underlying allergic condition and builds up an immunological tolerance to grass pollen by inducing immunological tolerance towards grass allergens. According to the summary of product characteristics, as a "Disease-modifying treatment of grass pollen induced rhinitis and conjunctivitis in adults and children (5 y or older), with clinically relevant symptoms and diagnosed with a positive skin prick test and/or specific IgE test to grass pollen".

GRAZAX®is in allergen extracts, grass pollens pharmacotherapeutic group, with the Anatomical Therapeutic Chemical (ATC) code V01AA02.

Mode of action

Specific Immunotherapy for allergy treatment has been used for more than 100 y. As previously mentioned, sublingual immunotherapy has only gained attention in the last three decades. There is a consensus that the aim of AIT is to induce allergen-specific peripheral tolerance by the periodic administration of the sensitizing allergen. Mechanisms described in relation to AIT effect include desensitization, T and B regulatory response generation, rebalance of Th1/Th2 responses, and interference of blocking antibodies (IgG4).[8] In a recent publication[9] it is described that oral mucosa undergoes a progressive remodelling associated to allergic inflammation. This impaired barrier function of the oral mucosa in allergic subjects constitutes an immunological access point for sublingual immunotherapy products. The sequence of treatment-induced changes in the later immunological events is analyzed in a prospective immunological mechanism study.[10,11] This study, carried-out for 5 y (3 of active

Table 1. Batch release specifications for GRAZAX®.

Test	Methods of analysis
Appearance	Visual examination
Uniformity of mass	Determination of mass of individual units
General test	Determination of disintegration time
General test	Water content (Karl Fisher)
Identity test	Protein profile (SDS-PAGE)
Potency	Total allergenic activity (TACA)
Potency	Major allergen content (ELISA) Phl *p* 5
Microbial enumeration	Membrane filtration (TYMC)
Test for specified microorganisms	Growth on media

therapy and 2 y follow-up), demonstrated that long-lasting benefit associated to the intervention is linked to the acquisition of an activated T cell memory regulatory phenotype. This response is generated progressively during the intervention and consolidated after 3 y of continuous treatment. Interestingly, recent studies have demonstrated that if GRAZAX® (or high-dose subcutaneous AIT) is administered only 2 y, this sustained benefit is lost.[12] Short-term effect (1–2 months) is generated by desensitization of effector cells, a mechanism that is not fully understood, antigen specific, and quickly lost after therapy discontinuation. Change in antibodies profile, linked to a progressive increase of specific IgG4, is seen after several months of therapy and reaches a peak during the first 2 y of treatment, with a high patient variability. In summary, these data support the need of continuous administration over a 3-year period, as stated in the marketing authorization of the product. In Figure 1 are summarized the immunological mechanisms involved in GRAZAX® effect.

Clinical development

According to the European regulatory guidelines on the clinical development of products for specific immunotherapy for the treatment of allergic diseases,[13] clinical efficacy evidence for seasonal allergies requires randomized double-blind, placebo-controlled (DBPC) long-term clinical trials. The following objectives have to be fulfilled:

- Treatment of allergic symptoms as clinical efficacy in first pollen season;
- Sustained clinical effect as maintenance of significant and clinically relevant efficacy during 2–3 treatment years;
- Long-term efficacy and disease-modifying effect as sustained significant and clinically relevant efficacy in post-treatment years (a minimum of 2 y after stopping immunotherapy);
- Curing allergy as sustained absence of allergic symptoms in post-treatment years.

GRAZAX® possesses the most complete and comprehensive series of clinical trials ever performed in specific AIT. With a total of 16 DBPC phase I–IIIb trials, in pediatric, adolescents, and adults, involving more than 7000 patients (>1700 aged 5–17-y old, >4400 adults), overall, GRAZAX® has set the clinical reference for future developments in AIT.

An example of design of 5-y trial is shown in Figure 2.

Phase I/II trials

Phase I/II trials incorporated 2400 patients and involved 124 clinical groups. The first study was performed in 52 subjects. Doses up to 75,000 Standardized Quality Units Tablets (SQ-T) were administered. In a second study, that involved 84 allergic patients 14, the tested dose was raised until 1,000,000 SQ-T. Cardiovascular system safety pharmacology was an integrated part of chronic repeat-dose toxicology study by electrocardiogram (ECG) and blood pressure measurements. No test-article-related effects on blood pressures or ECG patterns were detected. A further safety study was performed in 43 asthmatic patients. Fifteen of them received the maximum dose of 500,000 SQ-T. Phase I development was completed with two studies performed in children.[14]

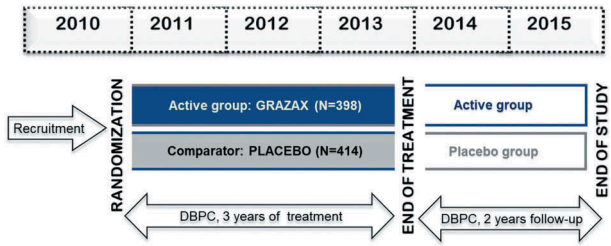

Figure 2. Example of a 5-y prospective clinical trial design.
GRAZAX® has three prospective 5-y studies on allergic rhinitis, asthma prevention, and immunological mechanisms.

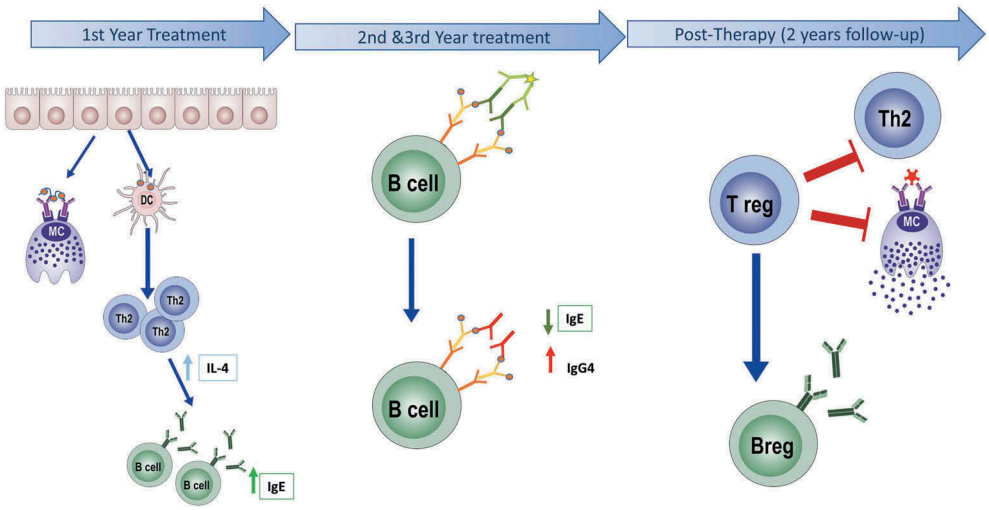

Figure 1. Scheme of the immunological response to allergen-specific immunotherapy (AIT). AIT during the early phase of the treatment (1–4 months), induces both mast cell desensitization and upregulation of Th2 response, mediated by high levels of IgE and IL4. During the active phase (1–3 y), a switch of isotype occurs. The levels of IgG4 increase while IgE significantly decrease. In this period is the maximum effect of IgG4 interference. Later, after 3 y of AIT treatment, in the post-therapy period, the regulatory response is established, and levels of IgE and IL4 are significantly decreased.

Overall, the product had an adequate safety/efficacy profile. A dose-/time-dependent serological antigen-specific response was reported. Most of the adverse drug reactions were local and mild and appeared during the first days of administration and faded in most of the patients after a week of treatment. No life-threatening reactions were observed. The adequate safety profile of GRAZAX® shown in these three studies allowed advance to further clinical research.

A pivotal Phase II trial in adults, with three administered doses, allowed the identification of the optimum therapeutic dose of 75,000 SQ-T.[15–17]

An additional safety and efficacy study on patients (n = 114) with mild-to-moderate asthma and rhinoconjunctivitis was performed. Safety in a severe patient subgroup was closely monitored.[18] The treatment was well tolerated and had a clear clinical benefit of symptoms/medication scores.

All the above-mentioned studies confirmed that the 75,000 SQ-T (GRAZAX®) dose provided the best risk-benefit profile.

Phase III trials

Pivotal Phase III trial: Pivotal trial was a multicenter, randomized, DBPC, parallel-group study, which aimed to confirm the efficacy of GRAZAX® in patients with seasonal rhinoconjunctivitis with or without mild-to-moderate asthma. A total of 634 grass-allergic patients were included in the study.

Treatment was initiated at least 16 weeks prior to the grass pollen season (GPS) and continued all year round, until the end of the GPS. The study was prolonged for two additional treatment years in about 50% of the subjects, and the effect was also assessed in a DBPC manner two additional years after treatment cessation.

Patients with clinical history of grass pollen–induced allergic rhinoconjunctivitis having received symptomatic treatment during the previous GPS, positive skin prick test against *P* pratense (Soluprick SQ; ALK), wheal diameter >3 mm; specific IgE against *P pratense*, IgE class 2; no clinical history of chronic sinusitis or perennial or seasonal allergic rhinitis and/or asthma because of another allergen during – or potentially overlapping – the GPS; no clinical history of severe asthma (Global Initiative for Asthma 2002 step 4 and FEV1 <80% of expected value after treatment with inhaled corticosteroids and short-acting b2-agonists); and no previous treatment by allergen-specific immunotherapy within the previous 5 y. Pregnancy was also an exclusion criterion.

Clinical efficacy was based in allergy symptom and medication scores. They were calculated as the sum of the individual daily scores for each subject during the GPS 2007 divided by the number of subject diary recordings of that score during the same period.

Each day subjects rated their rhinoconjunctivitis and asthma symptoms in the electronic diaries on a scale from 0 to 3 (0 = no, 1 = mild, 2 = moderate, 3 = severe symptoms). A total of 10 types of symptoms were rated. The six rhinoconjunctivitis symptoms were: runny nose, blocked nose, sneezing, itchy nose, gritty feeling or red/itchy eyes, and watery eyes. The four asthma symptoms were cough, dyspnea, wheezing, and exercise-induced asthma. In case of allergic symptoms, subjects had access to symptomatic relief medication (loratadine tablets, levocabastine eye drops, budesonide nasal spray, salbutamol spray, fluticasone inhaler, and prednisolone tablets) provided in a stepwise fashion depending on the persistence and severity of the symptoms. Use of relief medication was recorded in the daily diary and scored according to predetermined criteria.

This was the first prospective, 5-y clinical trial ever performed in AIT, and demonstrated that clinical benefit was established in the first treatment year, maintained during the two subsequent treatment years and persisted 2 y after discontinuation.[19,20] The effect size was comparable over the 5 y (Figure 3).

Other phase III trials

Pediatric indication was obtained in a DBPC study performed over a sample of 253 grass-allergic children (5–16-y old).[21]

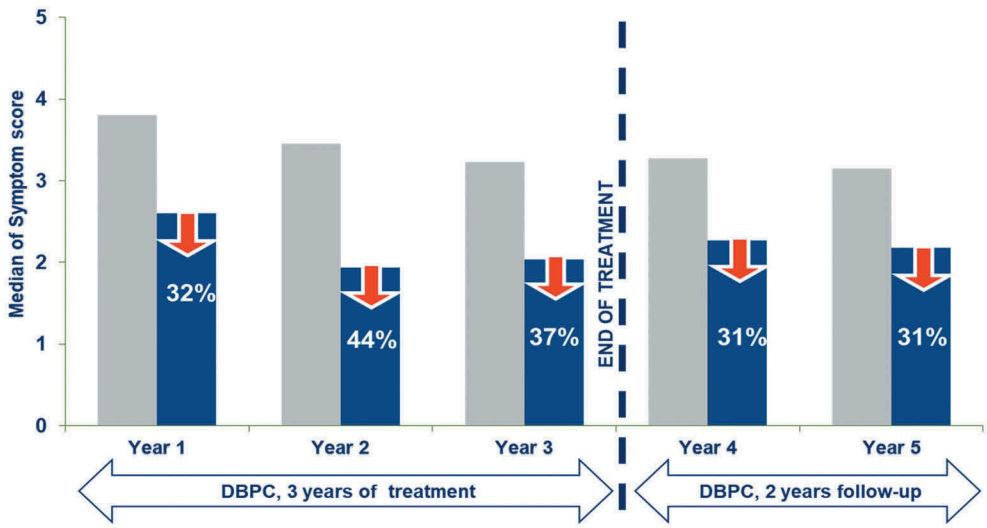

Figure 3. Clinical outcome of pivotal 5-y study.

Magnitude of the effect is similar during active treatment period, as well as during 2-y follow-up. However, underlying immunological mechanisms (Figure 1) greatly vary over the years. Grey bars represent placebo and blue bars represent active treatment.

The results confirmed same clinical benefit and immunological response as shown in adult studies.

Registration in North-America was gained with three DBPC studies, two of those Phase III trials performed in children, adolescents, and adults (5–65-y old), suffering from grass-allergic rhinitis with/without conjunctivitis and/or asthma, carried on in USA and Canada. A total of 1886 patients randomized 1:1 were included. Out of them, 85% were polysensitized and 25% had asthma. The results confirmed previous findings showing that GRAZAX® was effective in polysensitized grass-allergic North American children and adults with allergic rhinitis.[22,23]

As a summary, according to EMA guidelines on clinical development of products for specific immunotherapy, GRAZAX® has demonstrated clinical efficacy from the first GPS symptoms (as long as treatment is started 4 months before), sustained clinical effect during 3 y administration, and long-term efficacy (at least 2 y after discontinuation), being therefore a disease-modifying treatment.

Post-marketing authorization studies

Further clinical research as well as scientific evidence continue aftermarket authorization. More than 8700 patients have been exposed in 24 post-authorization phase IV and post-marketing surveillance studies. These studies have confirmed the safety profile of GRAZAX®.

In pharmacovigilance studies, safety-related variables were studied. Post hoc analysis from 13 GRAZAX® trials $n = 2497$; placebo, $n = 2139$ regarding epinephrine administrations in response to sublingual immunotherapy (SLIT)-tablet-related reactions were analyzed. The authors referred that epinephrine was used 13 times (grass SLIT-tablet, $n = 10$; placebo, $n = 3$). Eight administrations were associated with SLIT-tablet-related adverse events: four for systemic allergic reactions and four for local mouth and/or throat swelling. They concluded that epinephrine use is uncommon, typically occurs within the first week of treatment, and is rarely self-administered. All SLIT-tablet-related events treated with epinephrine were nonserious.[24]

The combined use of different AIT tablets was also investigated post-marketing. This is relevant because many patients are allergic to more than one allergen. In this trial, patients were allergic to both grass and ragweed, and dual administration of grass and ragweed SLIT tablets may be indicated for some of these patients. This multicenter open study including 102 patients found that after tolerability with single SLIT tablet administration has been established (4-week sequential tablet dosing schedule), dual treatment with GRAZAX® and ragweed SLIT tablets was well tolerated and could be followed by simultaneous tablet administration at home.[25]

Relevant scientific evidence like starting GRAZAX® treatment at any time of the year or even safety profile of intra-seasonal start of GRAZAX® in real-life setting show same tolerability as previously described in DBPC studies. Authors concluded that tolerability data for an intra-seasonal start of grass AIT during routine treatment confirmed the safety profile already known. The good tolerability was associated with high satisfaction and compliance.[26–28]

Attempts to improve compliance had been also reported post-marketing. Alesina et al. investigated if compliance can be increased by providing the patients an Compliance electronic device (CED) (Memozax; a tablet container with a programmable daily acoustic alarm). They showed that compliance to the treatment with AIT administered for 12 consecutive months is in general good (mean 83%). The use of CED was not associated with a greater compliance. AIT treatment was associated with a significant clinical improvement in >80% of patients with a good tolerability and safety profile.[29]

Other examples of research aftermarket authorization primarily focuses on clinical benefit more than tolerability. As an example, the influence of the duration of pre-seasonal treatment on clinical efficacy obtained within the GPS was investigated. Data from three multicenter randomized DBPC trials with different pre-seasonal treatment periods were analyzed. Authors concluded that GRAZAX® must be initiated at least 8 weeks prior to the GPS to provide significant clinical efficacy on the first GPS. Longer pre-seasonal treatment period (>8 weeks) improves the clinical efficacy (relative to placebo) during the GPS.[30]

Other important efficacy issue in clinical practice is related with the polysensitized condition of most pollen allergic patients. Thus, a post hoc analysis of pooled data from six randomized, DBPC trials ($n = 1871$) comparing the efficacy and safety of GRAZAX® in mono- and poly-sensitized subjects concluded that no difference in efficacy and safety of single-allergen grass AIT was observed between them.[31]

GAP (GRAZAX® Asthma Prevention) Study

The GAP trial represents the first 5 y prospective multinational, multicenter study performed in a randomized DBPC design aiming to investigate asthma prevention potential of AIT. It was performed in a pediatric sample of 812 allergic children suffering from rhinitis mediated by grass pollen, without asthma symptoms.

Both trial design and outcome are described in the first paper published of this trial.[32]

Trial design follows EMEA guidelines.[13] Other international treatment guidelines were also consulted on the different aspects of the study.[33–36] The primary end-point of the study, defined as the "difference in time to onset of asthma defined by pre-specified asthma criteria relying on documented reversible impairment of lung function," was not met.

However, there were multiple secondary end-points that supported the prevention potential of AIT. GRAZAX treatment significantly reduced the risk of experiencing asthma symptoms or using asthma medication at the end of trial (odds ratio = 0.66, $p < .036$), during the 2-y post-treatment follow-up and during the entire 5-y trial period. Additionally, it had a positive, long-term clinical effect on grass-allergic rhinoconjunctivitis symptoms that were 22–30% reduced ($p < .005$ for all 5 y). At the end of the trial, the use of allergic rhinoconjunctivitis pharmacotherapy was significantly lower in active treated patients (27% relative difference to 19% placebo, $p < .001$)[37]

An interesting finding was the significant decrease of winter asthma symptoms, a measure of bronchial hyperreactivity,

in treated patients, in the third winter of treatment, which persisted and increased in effect 2 y after discontinuation. This kinetic is in agreement with the acquisition of a memory T cell regulatory phenotype11 and supports the systemic benefit of early intervention in allergy.

We would like to finish the summary of clinical development of GRAZAX® showing the clinical implications stated in the GAP paper: "The data presented in this article demonstrate that treatment with the SQ grass SLIT tablet modifies the grass pollen allergic disease. The disease modification is expressed by preventing progression from allergic rhinoconjunctivitis symptoms to development of asthma symptoms and reducing rhinoconjunctivitis symptoms and medication use during and after treatment termination". In Figure 4 are summarized in chronological order the clinical trials performed in Europe.

Main clinical trials of GRAZAX® clinical development programme are summarized in Table 2.

Regulatory issues

GRAZAX® has been the first global AIT product registered following Pharmaceutical parameters. It has set the standard for future AIT product development.

Public-health

GRAZAX® has proved its pharmacoeconomic value. In an evaluation of its value,[43,44] it was concluded that GRAZAX® generated an incremental cost per quality-adjusted life year (QALY) of 12,168 GBP, and thus was a cost-effective option for the treatment of allergic rhinoconjunctivitis in a UK pediatric population. If we consider its preventive potential, this value will be further enhanced. In fact, AIT in general, and GRAZAX®, when administered following recommended schedule, has a unique therapeutic profile, as can modify the natural course of allergy.

Product availability

GRAZAX® is currently available in EU countries, Norway, Switzerland, US, Canada, Turkey, Russia, and Australia.

Advantages/disadvantages relative to other products

The only AIT product for grass allergy with a similar product design is ORALAIR®[45] Apart from the formulation, that has a clear influence in the product availability,[3,46] the main difference is that Oralair is recommended for pre-co-seasonal administration. As previously mentioned in the mode of action section, this administration schedule addresses mainly desensitization mechanisms, but might slow the generation of a regulatory response that is pivotal for sustained benefit.11 In fact, in a prospective 5-y trial, ORALAIR® showed a decline in the effect in the second follow-up study. Other difference between both products is based on the allergenic composition of GRAZAX® (one grass species) versus ORALAIR® (five grass species). Election of a single grass species was made in base to the high cross-reactivity observed in serological responses to different grass species.[47,48] In fact, in general, grass allergens present multiple isoforms, and thus a single species will incorporate different molecular variants of each allergen. Moreover, there is clinical evidence that a grass vaccine can be further simplified even to single isoform of

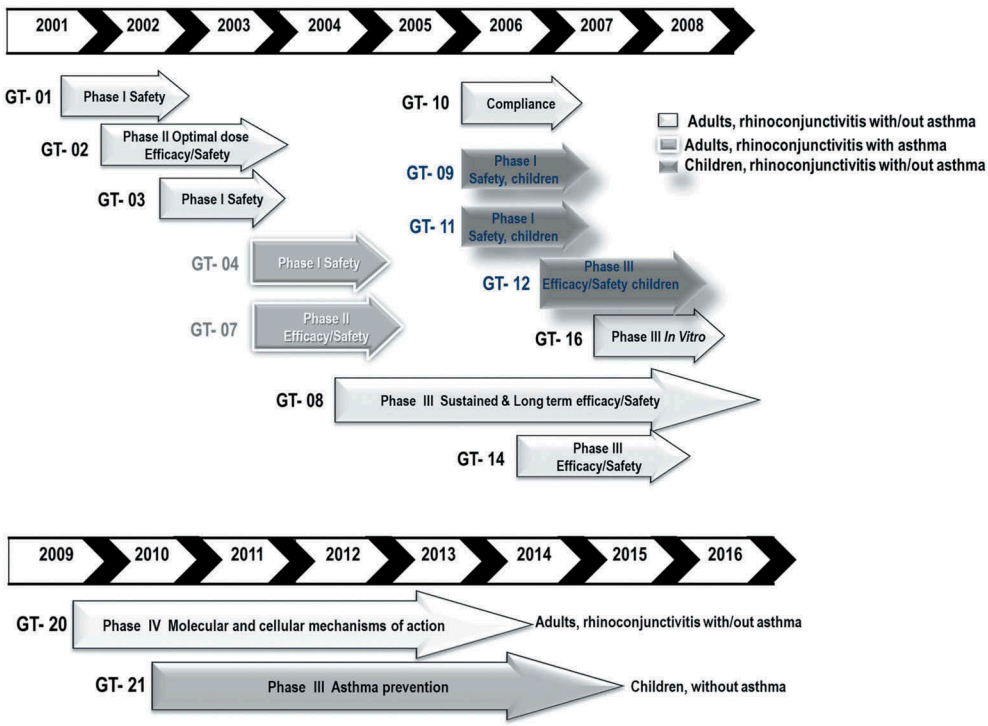

Figure 4. Summary of clinical trials performed in Europe.
GRAZAX® possesses the most complete and comprehensive clinical development programme ever performed in AIT.

Table 2. Summary of main Clinical trials performed with GRAZAX®.

Trials nomenclature	Population	Phase clinical development	Objectives	Disease, inclusion criteria	Doses	AIT duration	Country scope	Reference
GT- 01	Adults, $N = 52$	Phase I	Safety, dose finding	Allergic rhinitis	2500/25,000/75,000/125,000/375,000 SQ-T	23 weeks	Europe	38
GT- 02	Adults, $N = 855$	Phase II/III	Safety, dose finding	Allergic rhinitis	2500/25,000/75,000 SQ-T	24 weeks	Europe and Canada	15
GT- 03	Adults, $N = 84$	Phase I	Safety, dose finding	Allergic rhinitis	25,000/75,000/150,000/300,000/500,000/750,000/1,000,000 SQ-T	28 d	Europe	39
GT- 04	Adults, $N = 43$	Phase I	Safety, dose finding	Allergic rhinitis W/ WO Asthma	75,000/150,000/300,000/500,000 SQ-T	28 d	Europe	40
GT- 07	Adults, $N = 114$	Phase II	Safety, tolerability and efficacy	Allergic rhinitis W Asthma	75,000 SQ-T	20 weeks	Europe	18
GT- 08	Adults, $N = 634$	Phase III	short term efficacy, sustained effect, long term efficacy, safety and tolerability	Allergic rhinitis W/ WO Asthma	75,000 SQ-T	3y treatment + 2y follow-up	Europe	20
GT- 09 GT- 11	Children, $N = 60$	Phase I	Safety, tolerability	Allergic rhinitis W/ WO Asthma	75,000 SQ-T	28 d	Europe	14
GT- 12	Children and adolescents, $N = 253$	Phase III	Efficacy, safety and tolerability	Allergic rhinitis W/ WO Asthma	75,000 SQ-T	36 weeks	Europe	21
P05238	Adults, $N = 439$	Phase III	Efficacy, safety & tolerability	Allergic rhinitis W/ WO Asthma	75,000 SQ-T	24 weeks	USA and Canada	41
P05239	Children and adolescents, $N = 345$	Phase III	Efficacy, safety and tolerability	Allergic rhinitis W/ WO Asthma	75,000 SQ-T	25 weeks	USA and Canada	42
GT- 20	Adults, $N = 58$	Phase IV	Mechanism of action, immunological and cellular changes	Allergic rhinitis W/ WO Asthma	75,000 SQ-T	3y treatment + 2y follow-up	Europe	11
GT- 21	Children, $N = 812$	Phase III	Asthma prevention	Allergic rhinitis WO asthma	75,000 SQ-T	3y treatment + 2y follow-up	Europe	37

W: with; WO: Without.

relevant grass allergens.[49] Recently, it has been shown that some patients, mostly resident in the south of Europe, could have a higher sIgE recognition to a five species vaccine.[50] Currently, there is no evidence of clinical superiority in base to the number of grass species included in the vaccine composition.

Future product development needs

Allergen-specific Immunotherapy, when correctly used, is the only available pharmacotherapy with disease-modifying potential in allergic pathologies. Nearly 70% of the patients develop a sustained memory regulatory T cell response.[11] The problem is that there are no adequate biomarkers to monitor and predict successful AIT intervention. There is an urgent need to develop new biomarkers strategies.[51,52] New biomarkers, more connected to the disease, should allow not only monitor individual patient responses but also to compare different pharmacological interventions and prove the value of AIT intervention.

Grazax has set a clinical standard in AIT development. Better specific intervention strategies should be focused in obtaining long-term benefit after discontinuation with shorter treatment regimes, to increase patient compliance. This might be achieved for example by using better formulations or incorporating adjuvants in the formulation.

New prevention studies, with a focus on secondary prevention (asthma, poly-sensitization), should be developed with the lessons learned from the GAP trial.[32]

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

Funding

The present article has been supported by the Instituto de Salud Carlos III co-funded by the European Regional Development Fund "Investing in your future" for the thematic network and co-operative research centers ARADyAL RD16/0006/0009, RD16/0006/0015, RD16/0006/0026.

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