Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Phleum pratense (extract)

Proprietary Product Name: Grazax

Sponsor: Seqirus Pty Ltd

First round 30 April 2016

Second round 26 September 2016

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website < https://www.tga.gov.au>.

About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website < https://www.tga.gov.au/product-information-pi>.

Contents

List of abbreviations

Abbreviation	Meaning
AE	Adverse event
AIT	Allergy immunotherapy
ANOVA	Analysis of variance
ARIA	Allergic Rhinitis and its Impact on Asthma
BAU	Bioequivalent Allergy Units
BMI	Body mass index
CI	Confidence interval
CSR	Clinical study report
CTI	Cutaneous tolerance index
CPT	Conjunctival provocation test
DMS	Daily medication score
DSS	Daily symptom score
eCRF	Electronic case record form
FAP	Facilitated allergen presentation
FAS	Full analysis set
GCP	Good Clinical Practice
GINA	Global Initiative for Asthma
GPS	Grass pollen season
Grazax	Grazax 75,000 SQ-T oral lyophilisate, also called ALK grass tablet 75,000 SQ-T, also called SCH697243 (Timothy grass allergy immunotherapy tablet [2800 BAU *Phleum pratense* grass extract (equivalent to 75,000 SQ-T)]
ICAM-1	Intercellular adhesion molecule 1
ICH	International Conference on Harmonisation

Abbreviation	Meaning
IFNγ	Interferon Gamma
IgA	Immunoglobulin A
IgE	Immunoglobulin E
IgE blocking factor	Redefinition of the IgX term, calculated as: 1 – IgX; the IgE-blocking factor is thus a dimensionless number which varies theoretically from 0 (no presence of IgE-blocking components) to 1 (all IgE blocked from binding to allergen)
IgG	Immunoglobulin G
IgG4	Immunoglobulin G4
IgX	IgE-blocking antibodies/factor; IgX is the ratio between [allergen binding IgE-activity in serum measured in the presence of other serum components] and [allergen binding IgE- activity in serum measured in the absence of other serum components]. If no IgE-blocking factor is induced the IgX value is close to 1, whereas the presence of IgE-blocking factor will result in reduced IgX values. The assay is termed IgX since the isotype specificity of the competing components is not determined.
IgX assay	Assay designed to measure the inhibitory capacity of serum components competing with IgE for allergen binding. Assay read out is S/T. The assay is termed IgX since the isotype specificity of the competing components is not determined.
IL(-x)	Interleukin
IMP	Investigational medical product
LOCF	Last observation carried forward
MHC	Major Histocompatibility Complex
N	Number of subjects
NOS	Not otherwise specified (in relation to an adverse event)
Ph. Eur.	European Pharmacopoeia
PI	Product Information
PPD	Purified Protein Derivative derived from Bacillus Calmette-Guerin (BCG), (positive control)

Abbreviation	Meaning
Ph1 p1	A major allergen of *Phleum pratense* grass pollen
Ph1 p5	A major allergen of *Phleum pratense* grass pollen
PSUR	Periodic safety update report
SAE	Serious adverse event
SCH 697243	Grazax was trialled and sold by MSD, called Grastek in the USA
SCIT	Subcutaneous immunotherapy
SLIT	Sublingual immunotherapy
SmPC	Summary of product characteristics
SPT	Skin prick test
SQ	Standardised quality
SQ-T	Standardised quality units (tablet); the SQ-T and SQ-U units express the same biological activity. SQ-U was originally introduced for products for subcutaneous administration. The SQ-U has for Grazax been substituted by the unit SQ-T to distinguish between the 2 pharmaceutical forms (i.e. subcutaneous versus oromucosal use).
SQ-U	Standardised quality units, see SQ-T above
S/T	S (simultaneous) and T (2 step) describes how the analysis is performed. S: The IgE is present in the assay simultaneously with competing allergen specific antibodies T: No competing allergen specific antibodies are present in the assay. The readout from the assay that is S/T is a measure of the inhibitory capacity of serum components competing with IgE for allergen binding. Thus, a decrease in S/T signifies an increase in competing antibodies
TGF-β	Transforming growth factor β
TH1 or TH2	T-helper cells type 1 or 2
URTI	Upper respiratory tract infection
VAS	Visual analogue scale

Abbreviation	Meaning
VCAM-1	Vascular cell adhesion molecule 1
WHO	World Health Organisation

1. Introduction

This is a full submission to register a new biological substance.

Grazax is an allergen extract of grass pollen from Timothy grass (*Phleum pratense*).

The proposed indications are:

> *GRAZAX is allergy immunotherapy indicated for the treatment of grass pollen-induced allergic rhinitis with or without conjunctivitis.*
>
> *GRAZAX is indicated for disease-modifying treatment of grass pollen induced rhinitis and conjunctivitis.*
>
> *GRAZAX is approved for use in persons aged 5 years or older.*

The submission proposes registration of the following dosage form and strength:

- Allergenic extract of standardised grass pollen extract, Timothy grass (*Phleum pratense*) 75,000 SQ-T in pack sizes of 10, 30, 90 and 100 tablets.

2. Clinical rationale

The prevalence of allergic disease is increasing in most countries in the world and respiratory allergy is estimated to affect up to 50% of the population in some countries with an estimated 500 million sufferers in the world (Bousquet et al. 2008)[1]. Allergy to grass pollen is one of the most common inhalant allergies in the western world (Haahtela and Laitinen 1996).[2]

Allergic diseases are chronic conditions which account for a significant proportion of the overall health care costs in the industrialised countries. The expenses comprise both direct expenditures in the health care system and indirect costs associated with loss of productivity and impaired quality of life.

The treatment of allergic diseases is based on allergen avoidance, pharmaco-therapeutic symptom relief and specific immunotherapy:

Allergen avoidance has the purpose of creating a low allergen environment, for example in the subject's home, but for patients allergic to grass pollen this approach is not feasible

Symptom relief by conventional pharmacotherapy, for example antihistamines and topical and/or systemic steroid preparations, is available depending on the severity of the allergic disease. Despite the more recent introduction of the long acting, non-sedative antihistamines and the ready availability of steroid nasal sprays, such treatment often fails to produce sufficient symptomatic relief in up to 60% of subjects (White et al. 1998)[3]

Specific immunotherapy with allergen products is the repeated administration of allergens to allergic individuals in order to activate immunomodulatory mechanisms and provide sustained relief of symptoms and need for medications, and improvement in quality of life during subsequent natural allergen exposure.

[1] Bousquet et al. 2008 Allergic Rhinitis and its Impact on Asthma (ARIA) *Allergy* 2008: 63 (Suppl. 86): 8–160.
[2] Haahtela T and Laitinen L 1996, Asthma program in Finland 1994-2004. *Clinical and Experimental Allergy* 1996; 26: i-iii and 1-24.
[3] White P et al. 1998 Symptom control in patients with hay fever in UK general practice: how well are we doing and is there a need for allergen immunotherapy? *Clinical and Experimental Allergy* 1998; 28: 266–270

Seasonal allergic rhinoconjunctivitis to grass pollen may be considered a rather uncomplicated disease but it significantly influences and hampers a person's daily life and activities during the pollen season. Concomitant asthma is estimated to occur in 20 to 50% of patients with allergic rhinoconjunctivitis (Yawn et al. 1999)[4], and concomitant rhinoconjunctivitis is estimated to occur in more than 80% of asthmatic patients (Corren 1998).[5] Thus, allergic rhinitis and allergic asthma is considered different stages of the same allergic disease, consistent with the "one airway, one disease" theory (Bousquet et al. 2008; Grossman 1997)[1], [6] of allergy manifesting itself in different target organs (eyes, nose and lungs).

Long term strategies such as preventive measures and immunomodulatory treatment play an important role besides symptomatic treatment based on pharmacotherapy. Specific immunotherapy is the only treatment that affects the basic pathophysiological mechanism of the allergic disease and therefore the only available treatment that potentially has long-term efficacy and disease-modifying effect (Bousquet et al. 1998[7]; Durham et al. 2012[8]). In this context, the EU "Guideline on the clinical development of products for specific immunotherapy for the treatment of allergic diseases" (EMEA 2008) has defined disease modifying effect of specific immunotherapy in allergic rhinitis/rhinoconjunctivitis as sustained significant and clinically relevant efficacy in post treatment years.

Allergy immunotherapy (AIT) is a treatment option for allergy that is complementary to pharmacotherapy and with a distinct mechanism of action. AIT is performed by repeated sublingual (SLIT) or subcutaneous (SCIT, not the subject of this application) administration of specific allergens to an allergic person in order to gradually induce immunological tolerance towards the allergens. The objective of AIT is thus to treat the underlying allergic disease resulting in clinical effect on all manifestations of the disease. AIT modulates the basic immunologic mechanism of the allergic disease and is the only known treatment option with the potential to provide long term, post-treatment benefits and alter the natural course of allergic disease.

Comment: At the pre-submission meeting the TGA questioned the relevance of this product to Australia given that the product only contains *Phleum pratense* (Timothy grass) which is mainly found in the highlands of southern (temperate) Australia (parts of Tasmania and Victoria) and is considered a noxious weed.

To address this, the sponsor has provided additional information on *Phleum pratense* and a letter from Dr [Information redacted], Specialist in Clinical Immunology and Allergy and [information redacted].

The sponsor provides a statement that the Australian Virtual Herbarium (AVH) indicates the presence of Timothy grass in Victoria, NSW, Tasmania, South Australia and Western Australia. The reference to this is a website called AusGrass 2 ("Simon, B.K. & Alfonso, Y. 2011. AusGrass2, http://ausgrass2.myspecies.info/ accessed on 10 February 2016." The date of the reference to the AVH is 2011. When the AVH (AVH 2016. Australia's Virtual Herbarium, Council of Heads of Australasian

[4] Yawn BP et al 1999 Allergic rhinitis in Rochester, Minnesota residents with asthma: Frequency and impact on health care charges. J. Allergy Clin. Immunol. 1999; 103: 54-59
[5] Corren J 1998 The impact of allergic rhinitis on bronchial asthma. *J. Allergy Clin Immunol* 1998; 101: S352-356
[6] Grossman J 1997 One airway, one disease. *CHEST* 1997; 111:11S-16S
[7] Bousquet Jet al. 1998 WHO Position paper. Allergen immunotherapy: therapeutic vaccines for allergic diseases Geneva: January 27-29 1997.
[8] Durham SR et al. 2012 SQ-standardized sublingual grass immunotherapy: Confirmation of disease modification 2 years after 3 years of treatment in a randomized trial. *J Allergy and Clin Immunology* 2012; 129 ; 717-725

Herbaria, < http://avh.chah.org.au>, accessed 10 February 2016) was accessed directly it includes only NSW, ACT and WA as sites of presence.

Dr [Information redacted] provided the following comments:

"Timothy grass (*Phleum pratense*) is a member of the pooideae family, closely related to ryegrass and other common allergenic grasses known as the temperate grasses. Pooideae is a subfamily of poaceae which also includes subtropical grasses such as Bermuda grass (couch), bahia grass (paspalum) and sorghum. Timothy grass is itself not common or widely distributed in Australia although it does occur in cooler parts such as some parts of Victoria, Tasmania and the ACT. Ryegrass is probably the most widespread and common of the temperate allergic grasses. However it is known that Timothy grass contains almost all the relevant allergenic epitopes contained in ryegrass and other common temperate grasses. Therefore Grazax should be a suitable therapeutic product to treat allergy to Australian temperate grasses…Many sufferers of pollen allergy are sensitised to both temperate and subtropical grass pollens. In northern parts of Australia, it is thought that the primary (initiating) sensitising pollens are subtropical, and in the southern parts, temperate. It is thought that optimal immunotherapy should target the primary sensitising allergen and generally should cover all the major pollens to which the patients is sensitised

Therefore, it is unlikely that Grazax will be the optimal agent for pollen allergy sufferers in the northern parts of Australia, and in the southern parts where there is sensitisation to both temperate and subtropical grass pollens. However, it is likely to be a suitable agent for those with exclusive or predominant sensitisation to temperate grass pollens in the southern and central parts of Australia which constitute a significant subgroup."

3. Contents of the clinical dossier

3.1. Scope of the clinical dossier

The clinical dossier documented a development programme appropriate for a biological allergen product including pharmacology (limited), efficacy and safety studies.

Comment: The evaluator had concerns regarding the documentation of the dossier, particularly related to the lack of adequately indexed contents and description of clinical safety summary.

- All of the 17 clinical studies were included in Section 5.3.1; Reports of Controlled Clinical Studies.
- The evaluator considers that it would have been appropriate to report the studies : GT-16 and GT-18 the had primary objectives related to pharmacodynamics in Section 5.3.4 Reports of Human Pharmacodynamic Studies and 13 clinical studies in which the immunological parameters were measured in Section 5.3.5 Reports of Human Pharmacokinetic Studies
- The evaluator has noted that the Summary of Clinical Safety is lacking an integrated analysis but instead the safety data from each individual study was presented separately.
- The Summary of Clinical Efficacy identifies 7 studies that evaluated efficacy (GT-02, GT-07, GT-08, GT-12, GT-14, P05238 and P05239) but does not distinguish between adults and children. Study, UK22, is included in Section 5.3.5.4. This is a study of SC injection of a product called Alutard which is an extract of *Phleum*

pratense. This study was not evaluated as it is not relevant to the product for registration and is not discussed anywhere within the application.

- All the study reports were found to have at least 1 addendum, which included the narratives of deaths, other SAEs, withdrawals due to AEs, and other significant AEs and some appendices required translation.

The Clinical Overview presents the submission as containing the following clinical information:

- 1 x Phase IV study (GT-17)
- 9 x Phase III studies (GT-08, GT-10, GT-12, GT-14., GT-16, GT-18, GT-19, P05238 and P05239)
- 1 x Phase II/III study (GT-02)
- 1 x Phase II study (GT-07)
- 5 x Phase I studies, 3 in adults (GT-01, GT-04, GT-03), and 2 in children (GT-09 and GT-11)
- 2 x Phase III trials conducted by the applicant's partner in the US (P05238 (US adult) and P05239 (paediatric).

Five of these studies were done with a different formulation to the others – that is GT-01, GT-02, GT-03, GT-04 and GT-07. It is not stated what formulation was used in the partner studies (P05238 and P05239). The clinical study reports (CSR) state that the formulation is in the Investigator Brochure, which is not included in the submission). The Summary of Clinical Efficacy does not include all the studies in the submission (studies GT-10, GT-17 and GT-19 are not included). Although dated the same (October 2015) these studies are included in the Clinical Overview. No explanation is provided for this difference.

This report presents the data as follows:

- 2 x clinical pharmacology study that provided pharmacodynamic data (GT-16, GT-18). (PD data was also provided in many of the efficacy and safety studies.)
- 2 x dose finding studies (GT-01, GT-02)
- 2 x dose escalation studies (GT-03, GT-04)
- 2 x pivotal efficacy/safety studies in adults (GT-08, GT-14) – considered pivotal based on same primary endpoints and same formulation
- 2 x supporting efficacy studies in adults (GT-07, P05238)
- 1 x pivotal efficacy/safety studies in children (GT-12)
- 1 x supporting efficacy studies in children (P05239)
- 3 x other studies : efficacy/safety studies in adults (GT-10, GT-17, GT-19,)
- 2 x other efficacy/safety studies in children (GT-11 and GT-09)
- 2 x PSURs

The submission also included a Clinical Overview, Summary of Clinical Pharmacology, Summary of Clinical Efficacy, Summary of Clinical Safety and literature references.

3.2. Paediatric data

The submission included paediatric efficacy and safety data.

3.3. Good clinical practice

The clinical study reports state that the studies were conducted in accordance with the Declaration of Helsinki, the ICH guidelines on Good Clinical Practice and the applicable local regulatory requirements. Consent was obtained in writing prior to any trial-related activities.

4. Pharmacokinetics

4.1. Studies providing pharmacokinetic data

In accordance with the EMA Guideline on the clinical development of products for specific immunotherapy for the treatment of allergic diseases (CHMP/EWP/18504/2006; November 2008), traditional pharmacokinetic studies were not done as it is not possible for products of allergy immunotherapy. Due to the nature of the product (proteins which will be rapidly catabolised to peptides and amino acids), plasma levels of the active substance are not measurable.

4.2. Summary of pharmacokinetics

The information in the following summary is derived from selected literature references. It is not based on a formal literature based submission.

4.3. Physicochemical characteristics of the active substance

The following information is derived from the sponsor's summaries.

The drug substance in Grazax is a partly purified allergen extract of grass pollen from *Phleum pratense* (Timothy) which contains the relevant allergens. The drug substance is a mixture of molecules and the drug substance is standardised with respect to the content of major allergens. The biological activity is controlled by measuring the total allergenic activity and is expressed in the arbitrary Standardised Quality Tablet unit: SQ-T. However, the SQ-U unit is applied in protocols and reports because this unit has been used during development. The change from SQ-U to SQ-T is based on a wish from the applicant to make a differentiation between the subcutaneous treatment products (SQ-U) and the tablets (SQ-T).

4.4. Evaluator's overall conclusions on pharmacokinetics

The sponsor has not provided any clinical trials investigating the PK of the allergens in line with the EU guideline.

The information in the proposed PI is vague and not referenced but could be read as being based on clinical studies. It is suggested that this information be removed and a simple statement that no studies were conducted as is present in the overseas PI.

5. Pharmacodynamics

5.1. Studies providing pharmacodynamic data

Summaries of the pharmacodynamic studies were provided. Table 1 shows the studies relating to each pharmacodynamic topic.

Table 1: Submitted pharmacodynamic studies

PD Topic	Subtopic	Study ID	Primary Aim
Primary Pharmacology	Effect on immunological parameters	GT-01	Dose finding
	Adults	GT-02	Dose finding
		GT-03	Dose escalation
		GT-08	Efficacy and safety
		GT-14	Efficacy and safety
		GT-16	PD
		GT-18	PD
		P05238	Efficacy and safety
	Children	GT-09	Safety
		GT-11	Efficacy and safety
		GT-12	Efficacy and safety
		P05239	Efficacy and safety

None of the pharmacodynamic studies had deficiencies that excluded their results from consideration.

5.2. Summary of pharmacodynamics

Formal pharmacodynamic studies are not possible for allergen products.

The sponsor provided a summary of the PD based on selected literature references (not a formal literature based submission) and the results of immunological parameters from the two early phase and eleven efficacy and safety studies.

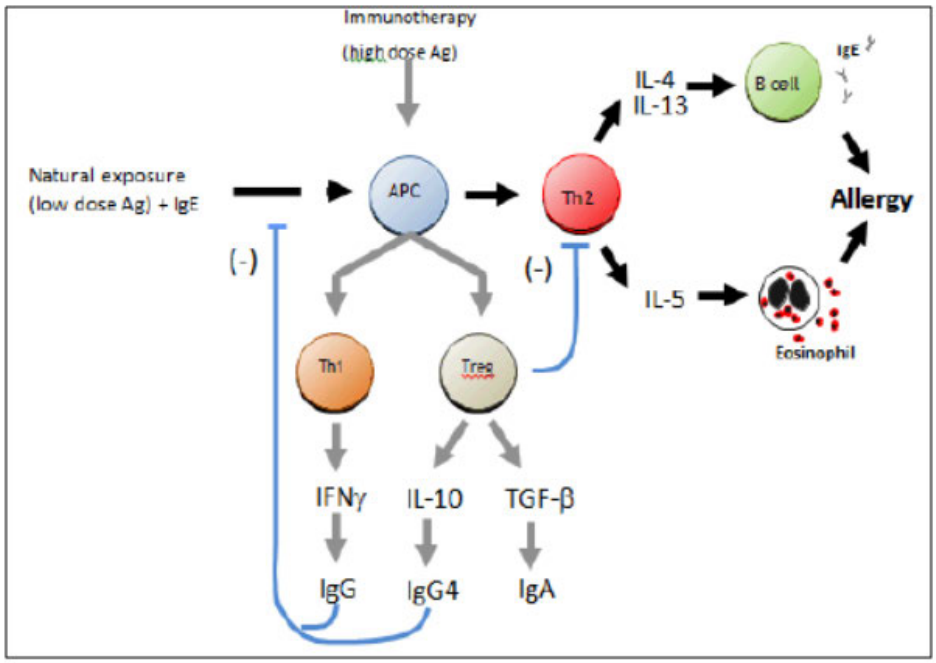
5.2.1. Mechanism of action

The immunological effect of specific immunotherapy is equivalent to a pharmacodynamic effect. Specific immunotherapy induces immune tolerance to the allergen to which the patient is allergic, and whether administered by means of injection or sublingually, specific immunotherapy has been shown to induce changes in T-cell responses (cellular immune responses) and antibody responses (humoral immune response) to the allergen. Essential clinical implications of induced and maintained immune tolerance after specific immunotherapy include prevention of new antigen sensitisation, prevention of progression to more severe disease and long term sustained effect after treatment cessation.

Several mechanisms by which specific immunotherapy acts have been proposed over time and the precise mechanism is still uncertain. Current data point towards an effect on allergen specific T-cells with immunoregulatory properties broadly referred to as regulatory T-cells

(Treg); this also involves a shift in the balance of allergen specific T-helper 1 (Th1) and T helper 2 (Th2) cytokine expression, as well as a change in the balance of allergen specific antibody expression.

Figure 1: Mechanisms of allergic versus healthy immune responses



Ag = allergen; APC = antigen presenting cell Allergic immune response to allergen (black arrow); specific immunotherapy probably acts by inducing a healthy immune response to allergen (grey arrow).

Two subgroups of CD4+ Treg cells seem particularly essential in suppressing the 'allergic' immune response to allergens: the naturally occurring thymus derived CD4+CD25+FOXP3+ Treg and the inducible IL-10 and/or TGF-β secreting type 1 Treg. Several other cells with suppressive or regulatory functions such as CD8+ Treg cells and regulatory natural killer (NKreg) cells have also been demonstrated.

The theoretical aims for allergen specific interventions can be summarised as follows:

- Down regulation or dampening of the existing Th2 response resulting in a state of non-responsiveness of the CD4+ Th2 cells termed 'anergy'
- Up-regulation or enhancing of the Th1 response that essentially does not affect the existing CD4+ Th2 response but changes the balance between the two to a predominant Th1 cell type
- A shifting of existing CD4+ Th2 cells to Th1 cells known as 'immune deviation'
- Generation of Treg cells, thereby inducing and maintaining a peripheral T-cell tolerance through a change in the Th2/type 1 Treg cell balance involving a shift in the balance of Th1 and Th2 cytokine expression.

A major clinical effect of specific immunotherapy is the reduction of inflammatory responses in the mucosa of the affected target organ. This effect is in agreement with reduced numbers and reduced activity of inflammatory cells observed in the mucosa following treatment.

Serological trials of specific immunotherapy have established that successful treatment is accompanied by an increase in allergen specific IgG. IgG is thought to inhibit binding of IgE to allergen in a competitive manner. The isotype of IgG is predominantly IgG4, but early in treatment IgG1 is also prevalent. To account for all treatment induced blocking components (that is IgG isotypes, IgA and other less defined components), the applicant has developed a

method to determine the effect of all allergen specific IgE-blocking components (termed IgE-blocking factor) in serum based on 2 determinations of IgE:

1. the total amount of IgE that bind to allergen in the absence of competing components, and
2. the amount of IgE that bind to allergen in the presence of competing components.

IgE-blocking factor varies theoretically from 0 (no presence of IgE blocking components in serum) to 1 (all allergen specific IgE antibodies are blocked from binding to allergen in serum).

5.2.2. Pharmacodynamic effects

5.2.2.1. Primary pharmacodynamic effects

Immunological parameters were assessed as part of the following studies (Table 2)

Table 2: Studies in which immunological parameters were assessed

Study	IgE	IgA	IgG4	IgX*	Others
Adults					
Study GT-01	Y	Y	Y	Y	T cell responses
Study GT-02	Y	Y	Y	Y	
Study GT-03	Y			Y	
Study GT-08	Y		Y	Y	
Study GT-08 extension	Y		Y	Y	facilitated allergen presentation (FAP, Years 1-3 and Year 5)
Study GT-14, GT-18 and PO5238	Y		Y	Y	
Study GT-16	Y		Y	Y	Skin reactivity
Children					
Study GT-09, GT-11 and GT-12	Y		Y	Y	
Study P05239	Y		Y	Y	

* IgX = IgE blocking antibodies/factors

The responses in each trial were included in summaries of the individual trials.

Changes in allergen specific serum antibodies were generally consistently observed. An initial rise in IgE levels was seen followed by a plateau/slow decrease. Simultaneously a slower increase in IgG (particularly IgG4) was observed. IgG is able to compete with IgE in binding to the allergens and this was observed in different in vitro assays as a blocking effect (termed IgX/IgE-blocking antibodies/IgE-blocking factor).

In Study GT-03 by mistake, no blood samples for analysis of immunological parameters were collected at the end of the trial. Therefore the immunological analyses are limited to clarify

whether an effect on serological parameters was detectable one year after the end of the treatment period. 70 serum samples were obtained; 17 from placebo subjects and 53 from actively treated subjects (all doses). The results indicated that it was not possible to detect a significant long-term effect on the levels of antibodies (*Phleum pratense* specific IgE, IgE-blocking antibodies, and total IgE) measured 1 year after a short treatment period (28 days) with different doses of Grazax.

In Study GT-08 extension the differences to placebo in increase from baseline in IgG4 and IgE-blocking factor were shown to be significant 2 years after completion of 3 years of treatment. However, as antibody production is dependent on presence of specific antigen, the difference between groups is less pronounced when treatment is stopped.

The immunological changes observed in children followed the same pattern as in adults. In Study GT-12 a clear induction of IgG4 and of IgE-blocking antibodies was observed for the children treated with Grazax, and the difference in treatment effect between the Grazax group and the placebo group was statistically significant. For IgE antibodies, the rise experienced by the placebo group during the grass pollen season was blunted for the Grazax group. In the US paediatric Study P05239, the results from the immunological measures demonstrated overall a significant increase in IgE, IgG4, and IgE blocking factor. Specifically *Phleum pratense* specific IgG4 and IgE-blocking factor showed a substantially larger immunological response in subjects treated with Grazax compared to placebo. All these observations were in line with observations from the Grazax trials in adults, although in the paediatric trials there seem to be less difference in specific IgE between active and placebo at the end of the grass pollen season, due to a more pronounced seasonal IgE increase in the paediatric placebo groups.

The changes seen in subcutaneous and sublingual immunotherapy are qualitatively similar. However, a direct comparison must be performed with some caution. Based on experience with vaccination against pathogens it must be assumed that sublingual immunotherapy (that is mucosal vaccination) is more effective in inducing immunological effects at mucosal surfaces and less effective in producing a serum antibody response than subcutaneous immunotherapy.

5.2.3. Pharmacodynamic interactions

No interactions studies were conducted.

5.3. Evaluator's overall conclusions on pharmacodynamics

There were no studies in this dossier with PD endpoints. This submission included studies that measured immunological parameters. The sponsor has considered the immunological effect of specific immunotherapy as a surrogate measure of pharmacodynamic effects.

In the studies that measured immunological parameters changes in allergen specific serum antibodies were observed, although not quite as consistently as the sponsor claims.

IgE-blocking antibodies (IgX) have been suggested a possible marker for clinical efficacy of specific immunotherapy. The median ratio of *Phleum pratense* specific IgX showed a decrease in the median value of the active treatment group after 4 weeks of treatment. Thus, the treatment led to higher activity of IgE-blocking antibodies.

Overall, a time and dose dependent response was shown for the IgG and IgE antibodies analysed in blood, indicating that the treatment had an effect on the immune system.

6. Dosage selection for the pivotal studies

Two dose finding and two dose escalation studies were conducted to establish the safety and optimal dose of the allergens for the pivotal studies.

Study GT-01 was a randomised double blind placebo controlled safety trial with an 8 week dose escalation phase, followed by an optional 15 week parallel treatment group phase. Forty-four subjects completed the initial phase of the trial, and 28 subjects completed the parallel treatment group phase. Three different dose groups were included in the parallel treatment group phase (2,500 SQ-T, 25,000, 75,000 SQ-T). Subjects were between 18 and 65 years of age and had seasonal allergic rhinoconjunctivitis with confirmed sensitivity to *Phleum pratense*. The results indicated that the doses 2,500 SQ-T, 25,000 SQ-T and 75,000 SQ-T were considered safe for further investigation in future clinical trials.

The primary objective of the GT-02 trial was to evaluate the efficacy of specific immunotherapy with 3 doses of Grazax, 2,500, 25,000 SQ-T and 75,000 SQ-T, compared to placebo, in adult subjects with grass pollen induced allergic rhinoconjunctivitis receiving active rescue medications as needed. The results indicated that the 75,000 SQ-T dose was the only dose demonstrating a clinical effect and statistically significant differences compared to placebo.

Study GT-03 was a randomised, double blind placebo controlled multiple dose, dose escalation Phase I safety trial with a 28 days treatment period in 84 subjects. Eight dose groups received treatment with Grazax (25,000, 75,000, 150,000, 300,000, 500,000, 750,000 or 1,000,000 SQ-T) or placebo, daily for 28 days. Due to an error in the conduct of the trial, no blood samples were taken at the end of the trial and consequently evaluation of treatment induced response was not possible. Blood samples were taken 6 to 12 months after treatment. The long-term effect on the levels of antibodies (*Phleum pratense* specific IgE, IgE-blocking antibodies, and total IgE) measured one year after a short treatment period (28 days) with different doses of Grazax was evaluated however, no significant long-term treatment effect was observed. A clear dose dependent increase in the overall rate of treatment related AEs and in the incidence of 'gastrointestinal symptoms' (including most oral sensations) was observed. The increase for treatment related AEs as well as 'gastrointestinal symptoms' started at 75,000 SQ-T.

Study GT-04 was a double blind, parallel group, placebo controlled trial to evaluate the safety of Grazax in the dose groups 75,000, 150,000, 300,000 and 500,000 SQ-T in 43 subjects. The incidence of AEs appeared to be dose related but the relation was not pronounced, however the number of AEs reported in the 75,000 SQ-T groups was distinctly lower compared with the higher dose levels.

In children, the tolerability of 75,000 SQ-T was investigated in two Phase I trials (GT-09 and GT-11). No indications of any significant differences between the adult and the paediatric population were observed and this was in agreement with the well-established clinical practice of using the same dosage of immunotherapy in adults and children.

In conclusion, as safety is of utmost importance for a product intended for home treatment, an efficacy size markedly above what has already been seen in the GT-07, GT-08 and GT-12 trials probably is unrealistic for the first year with any immunotherapy treatment; the 75,000 SQ-T dose was recommended. An increased dose could lead to more AEs and thereby potentially compromise the benefit-risk profile. In addition, reduced subject compliance to the treatment due to tolerance problems at the application site could undermine the treatment regimen. In conclusion, the 75,000 SQ-T dose compared to other doses was considered having an optimal benefit-risk profile.

7. Clinical efficacy

Indication 1: Treatment of allergic rhinitis with or without conjunctivitis in adults

Comment: In many of the studies the effect of treatment on asthma was evaluated. As asthma is not included in the indication being requested, the results for asthma are not presented in detail in this report.

7.1. Pivotal efficacy studies

7.1.1. Study GT-08

A randomised, parallel group, double blind, placebo controlled Phase III Trial Assessing the efficacy and safety of ALK Grass tablet *Phleum Pratense* in subjects with seasonal grass pollen induced rhinoconjunctivitis.

Comment: The evaluator has concerns about the following aspects of the study report:

- Instead of a single report of data comprising the whole study period, this study report consisted of 12 parts, which included a report and an addendum for every 5 years of the study period.
- There were study amendments that were initiated by the errors in the original report.[9]
- An integrated summary of the study was lacking in the dossier. This was particularly concerning since the primary objective varied during the course of the entire study period. For convenience, the primary objective of the study is taken from the first CSR and the secondary objectives include the objectives (primary and secondary) from the subsequent year CSRs.

These aspects limited the ability to perform a comprehensive efficacy assessment.

7.1.1.1. Study design, objectives, locations and dates

A randomised, parallel group, double blind, placebo controlled study conducted at 51 sites in 8 countries in Europe (Austria, Denmark, Germany, Italy, Netherlands, Spain, Sweden and the UK) from September 2004 to September 2009.

Primary Objective

To evaluate the efficacy of specific immunotherapy with the 75,000 SQ-T ALK grass tablet compared to placebo in subjects with grass pollen induced rhinoconjunctivitis, based on the rhinoconjunctivitis symptom score as well as the rhinoconjunctivitis medication score during the grass pollen season 2005 (Year 1) and in subsequent Years 2006 to 2009 (extension study).

Secondary Objectives

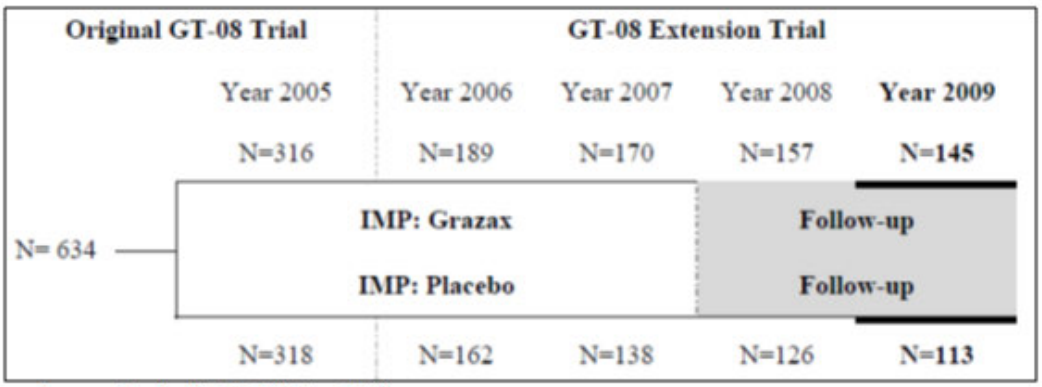
- To evaluate the efficacy of specific immunotherapy with the 75,000 SQ-T ALK Grass tablet compared to placebo in subjects with grass pollen induced rhinoconjunctivitis during the grass pollen season 2005 based on:
  - Rhinoconjunctivitis symptom and medication score during the peak grass pollen season 2005
  - Quality of Life (QoL) in the entire grass pollen season 2005
  - Number of well days in the entire grass pollen season 2005 and in the peak grass pollen season 2005 (well day = no rescue medication and symptom score ≤ 2)
  - Rhinoconjunctivitis symptoms on visual analogue scale (VAS)
  - Global Evaluation of rhinoconjunctivitis symptoms in the grass pollen season 2005
  - Global Evaluation of rhinoconjunctivitis symptoms in the grass pollen season 2005 compared to symptoms in the grass pollen season 2004
  - Excellence of rhinoconjunctivitis control during the entire grass pollen season 2005 (excellent rhinoconjunctivitis control = more than 50% well days in the grass pollen season).

[9] Clarification; see evaluator's comment in Section 7.1.1.12- Results for the primary efficacy outcome

- To evaluate the efficacy of 2 and 3 years of treatment with the 75,000 SQ-T ALK Grass tablet compared to placebo in subjects with grass pollen induced rhinoconjunctivitis. Efficacy was evaluated at the end of each grass pollen season 2006 and 2007 based on the secondary efficacy endpoints.
- To evaluate the persistent efficacy of 3 years of treatment with the 75,000 SQ-T ALK Grass tablet compared to placebo in subjects with grass pollen induced rhinoconjunctivitis. Persistent efficacy was evaluated at 4 and 5 years after initiation of treatment (end of each grass pollen season 2008 and 2009) based on the secondary efficacy endpoints.
- Changes in immunological blood markers based on the secondary efficacy endpoints
- Prevention of asthma based on FEV1, adverse events, asthma symptom and medication score.

The trial was initiated in the autumn 2004 and subjects received Grazax or placebo 4 to 8 months prior to the grass pollen season and during the grass pollen season 2005. At the end of the initial study the participants were offered continued treatment for an additional 2 years (then extended to 3 years with an additional 2 years of follow up).

Figure 2: Study GT-08: Overall Trial Design



Source: Study GT-08 CSR Panel 5-1

7.1.1.2. Inclusion and exclusion criteria

Inclusion

Healthy males or females (non-childbearing potential) aged 18 to 65 years with a clinical history of grass pollen induced allergic rhinoconjunctivitis of 2 years or more requiring treatment during the grass pollen season; a clinical history of severe rhinoconjunctivitis symptoms (interfering with usual daily activities or sleep), which remain troublesome despite treatment with anti-allergic drugs during the grass pollen season; a positive Skin Prick Test (SPT) response (wheal diameter ≥ 3 mm) to *Phleum pratense* and positive specific IgE against *Phleum pratense* (≥ IgE Class 2)and FEV1 ≥ 70% of predicted value.

Exclusion

A clinical history of symptomatic seasonal allergic rhinitis and/or asthma due to tree pollen or weed pollen adjacent to the start of, and potentially overlapping, the grass pollen season; clinical history of significant symptomatic perennial allergic rhinitis and/or asthma caused by an allergen to which the subject is regularly exposed; clinical history of significant recurrent acute sinusitis (defined as 2 episodes per year for the last 2 years all of which required antibiotic treatment) or chronic sinusitis; current symptoms of, or treatment for, upper respiratory tract infection, acute sinusitis, acute otitis media or other relevant infectious process (serious otitis media is not an exclusion criterion); history of emergency visit or admission for asthma in the previous 12 months.

7.1.1.3. Study treatments

During the treatment phase Year 2005 the subjects were randomised to receive double blind active treatment (75,000 SQ-T grass pollen extract) or placebo taken once daily, preferably in the morning. The tablet was placed under the tongue and swallowing to be avoided for 1 minute. Eating and drinking was not allowed within 5 minutes after study drug intake. First dose was taken at the clinic and the subject stayed at the clinic for 60 minutes for observation. Following doses were taken at home. Treatment was for total of 3 years.

Rescue medication

Rescue medication for rhinoconjunctivitis was provided in the following steps:

- Step 1: Desloratadine 5 mg tablets. Dosing: 1 tablet daily prn.
- Step 2: Budesonide nasal spray 32 µg micronised budesonide per actuation. Dosing: Up to 2 actuations per nostril twice daily, prn.
- Step 3: Prednisone 5 mg tablets. Dosing: Up to 50 mg daily for 3 days.

Step 1 and 2 rescue medications were dispensed to the subject at the pre-season visit (Visit 5). However, Step 2 rescue medication was only to be taken if symptoms were not satisfactorily controlled by ALK Grass tablets and Step 1 medication. If symptoms were not satisfactorily controlled by Step 1 and Step 2 rescue medication as evidenced by a minimum symptomatology, defined as a total score of the nose/eye symptoms of 4 or above the subject called the centre for an unscheduled visit where the investigator confirmed the symptomatology and if confirmed prescribed up to 50 mg prednisone orally at the time of the visit and supplied prednisone for the next 2 days as an "add-on to Step 1 and Step 2 rescue medication.

The rescue medication for rhinoconjunctivitis was scored as follows (Table 3)

Table 3: Study GT-08 rescue medication for rhinoconjunctivitis scores

Medication Step	Score/Dose [1].	Maxscore/Day
1 Desloratadine - 5 mg/1 tablet daily	6 (per tablet)	6
2 Budesonide nasal spray - 32 µg/puff up to 2 puffs per nostril twice daily	1 (per puff)	8
3 Prednisone – 5 mg/tablet up to 10 tablets (50 mg) once daily	1.6 (per tablet) [2]	16
Max. daily rhinoconjunctivitis medication score		*30*

1) Scoring scales were not seen by the subjects
2) Use of prednisone counted in the rhinoconjunctivitis score and/or in the asthma score depending on the symptoms.

7.1.1.4. Efficacy variables and outcomes

The primary efficacy outcomes were the average rhinoconjunctivitis symptom score (DSS) as well as the average rhinoconjunctivitis medication score (DMS).

Other efficacy outcomes included:

- Rhinoconjunctivitis symptoms scored on VAS
- Number of well days
- Global evaluation of rhinoconjunctivitis symptoms
- Immunological markers
- Quality of Life Assessments – determined using the Juniper's Rhinoconjunctivitis Quality of Life (RQLQ).

Details of outcome measures and evaluation scores were provided.

7.1.1.5. Randomisation and blinding methods

Randomisation was performed in blocks [unstated size] using a computer generated randomisation list. The trial was double blinded with the placebo tablets being similar to the tablets containing grass pollen extract with respect to appearance, smell and taste.

7.1.1.6. Analysis populations

Full Analysis Set (FAS) = all subjects randomised.

Per-Protocol Set (PP) = subjects without major protocol deviations (defined as subjects who did not take prohibited medication, had sufficient pre-seasonal treatment defined as at least 20 weeks treatment prior to the start of the pollen season, had sufficient study drug compliance defined as at least 80% and sufficient diary data defined as at least 50% of diary data in the pollen season).

7.1.1.7. Sample size

The power calculation was based on the average rhinoconjunctivitis symptom score during the grass pollen season. Data of average rhinoconjunctivitis symptom score in the grass pollen season necessary for the calculations were estimated from previous trial data (GT-02). The values used were: mean symptom score 2.91 and SD 2.25. This resulted in SD/mean of 0.8 (2.25/2.91 = 0.8). Consequently, the sample size calculation, based on a 2-sided, 2 group t-test of equal means, and a 5% significance level (SD/mean set to 0.8) gave the results shown below (Table 4).

Table 4: Study GT-08 sample size calculation

POWER	*active* = 0.85 * *placebo* (Difference = -15%)	*active* = 0.80 * *placebo* (Difference = -20%)	*active* = 0.75 * *placebo* (Difference = -25%)	*active* = 0.70 * *placebo* (Difference = -30%)
80%	448	253	162	113
90%	599	338	217	151
95%	741	417	268	186

Sample size calculation using nQuery Advisor

A reduction of at least 25% in symptoms could be found with a 5% significance level and a power of 95% if the sample size without drop-outs should include 268 subjects in each arm. With a 10% dropout approximately 300 subjects need to be included in each treatment arm.

7.1.1.8. Statistical methods

The endpoints used in this analysis were average rhinoconjunctivitis symptom score as well as the average rhinoconjunctivitis medication score. As two comparisons were evaluated the approach to the multiple comparisons issue was a hierarchical ordering of the null hypotheses. Hence, no statistical conclusions were based on test of a null hypothesis that had a rank lower than or equal to the null hypothesis that was the first not to be rejected. The ranking of the null hypotheses was as follows:

1. 75,000 SQ-T versus placebo on rhinoconjunctivitis symptom score
2. 75,000 SQ-T versus placebo on rhinoconjunctivitis medication score.

As the ranking of null hypotheses was pre-specified no formal adjustment of the statistical significance was necessary. The primary investigation of the comparison of the 2 treatment groups was done via an analysis of variance (ANOVA) with the average rhinoconjunctivitis symptom score or the average rhinoconjunctivitis medication score as response variable, treatment group as a fixed effect, pollen region as random effect, and adjustment for different error variation for each treatment group. A 2-sided 95% CI for the difference in adjusted means between the 2 groups is presented as well as the coherent p-value. Also, the difference in adjusted means between the 2 treatment groups relative to the adjusted mean of the placebo

group is presented as a percentage. A p-value describing the statistical significance of the pollen region is also presented.

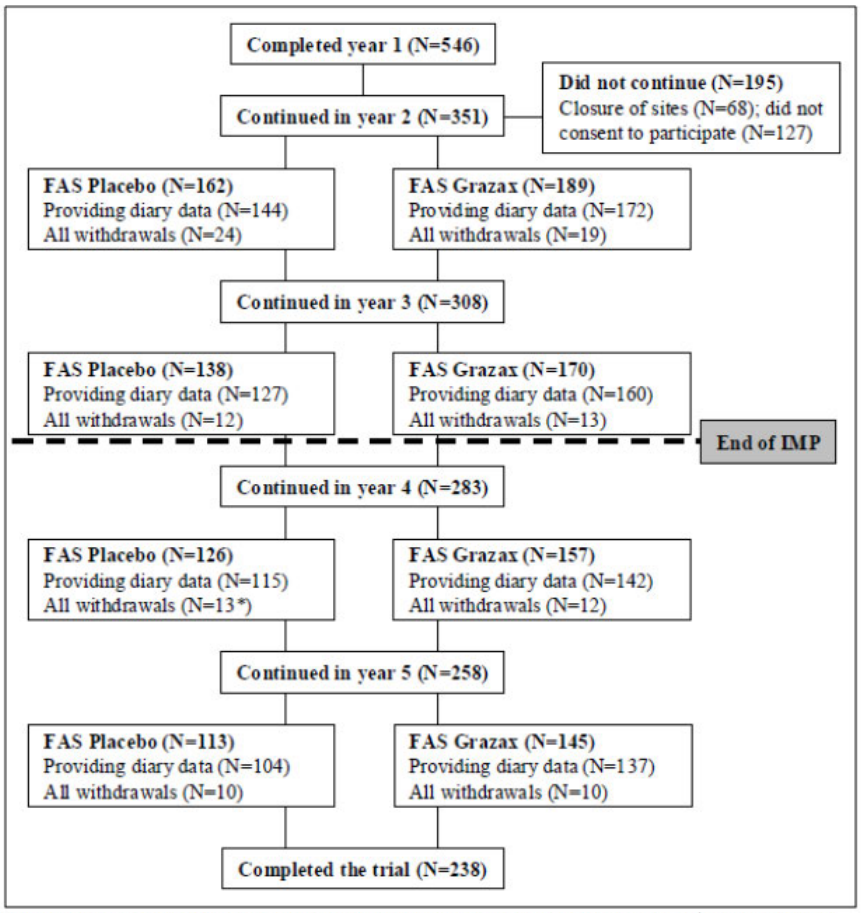
7.1.1.9. Participant flow

Table 5: Study GT-08: Summary of subject disposition; Year 1

Treatment Group	75,000 SQ-T		Placebo		Overall	
	N	%	N	%	N	%
Screened					888	
Full Analysis Set	316	100	318	100	634	100
Completed Year 1	274	87	272	86	546	86
Withdrawn from Year 1	42	13	46	14	88	14
Reasons for withdrawal:						
Adverse event	16	5	8	3	24	4
Death					1*	0
Lack of efficacy					1	0
Lost to follow-up	5	2	7	2	12	2
Other	6	2	14	4	20	3
Pregnancy					3	0
Subject non-compliance	4	1	10	3	14	2
Withdrawal of consent	9	3	4	1	13	2
Withdrawal initiated by:						
Investigator	8	3	9	3	17	3
Sponsor	3	1	8	3	11	2
Subject	31	10	29	9	60	9
Continued in extension	188	59	163	51	351	55

N=number of subjects, %=percent of subjects, * not related to IMP,
Source: Study GT-08 CSR Year 1 (EOT Table 1.1)

Figure 3: Study GT-08: Participant flow and analysis sets; 5 years



*: For 3 subjects in the placebo group the trial completion page was not collected until the 5th year of the trial, thus in the 4th year CSR these subjects were counted as continuing in the trial.
Source: Study GT-08 Year 5 Panel 7-1

7.1.1.10. Major protocol violations/deviations

Two subjects had major violations of the protocol (forgetting to take study drug for 3 weeks and taking prohibited medication) and at 2 sites all patients took Step 1 and 2 rescue medication incorrectly. Eleven subjects had major procedural deviations mostly related to taking incorrect rescue medications. The consequences of the deviations are judged by the sponsor to be insignificant and not to compromise the overall trial outcome.

7.1.1.11. Baseline data

No major differences between treatment groups in anthropometrics and vital signs were seen at baseline. The data for the general subject population was within the normal range.

The trial population comprised slightly more males (59%) than females (41%). The subjects had moderate (44%) or severe (56%) allergy to grass pollen and had a mean duration of grass pollen allergy of 16 years. The majority of subjects were Caucasian (96%), with Asian (2%), African (1%) and other (2%).

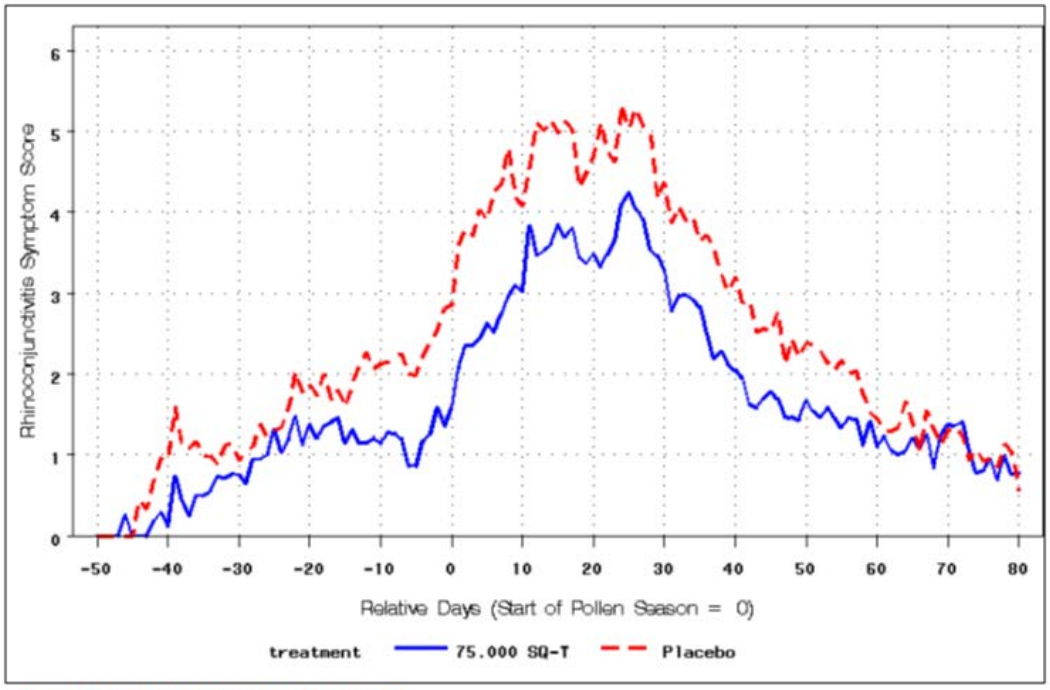
Tabulated results were provided.

7.1.1.12. Results for the primary efficacy outcome

Comment: The results for the primary efficacy outcome in the original report were found to be in error due to a programming error relating to the imputation of missing data. In the original report due to a programming error in the electronic diary used by the patients, missing data was assigned the number "0" instead of being disregarded in the calculation of the mean symptom and medication score. This error influenced the major part of the efficacy endpoints. To correct this, the sponsor provided an amended CSR called Amendment 1. The Amendment 1 report was used to provide the results in this report. A second programming error in the analysis of the RQOL was also corrected. The analysis should have been restricted to the period of the pollen season according to the pre-specified Statistical Analysis Plan. Instead all data from the weekly electronic diary with RQOL data were used, that is including data before and after the grass pollen season. The original report was dated 24 October 2005 and the Amendment 1 report was dated 6 December 2006.

The primary objective was to compare the efficacy of specific immunotherapy with the ALK Grass tablet 75,000 SQ-T to placebo based on the rhinoconjunctivitis symptom score as well as the rhinoconjunctivitis medication score during the grass pollen season 2005.

Figure 4: Study GT-08: Average daily rhinoconjunctivitis symptom score



Source: Study GT-08 CSR Amendment 1 Figure 9-1

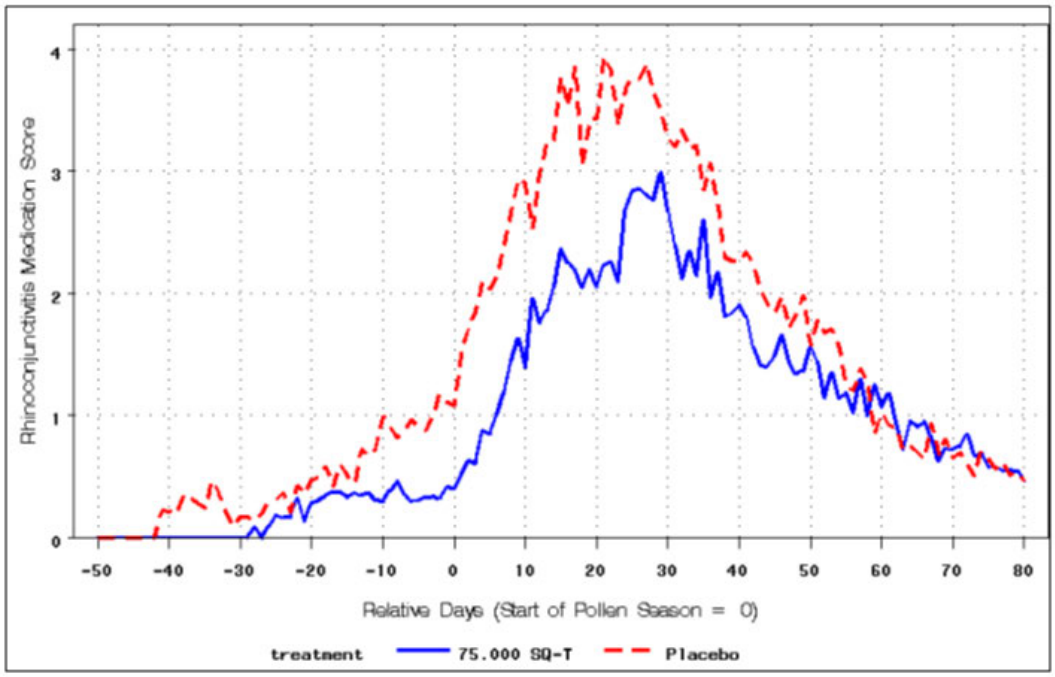
The descriptive comparison of the ALK Grass tablet and placebo showed that subjects treated with the ALK Grass tablet had fewer symptoms than subjects treated with placebo. This was evident on both nose and eye symptoms during the grass pollen season as well as the peak pollen season.

Table 6: Study GT-08: Summary of average daily rhinoconjunctivitis symptom score during the pollen season (FAS)

Treatment Group	75,000 SQ-T	Placebo	Overall
Number of Subjects	316	318	634
Entire Grass Pollen Season:			
N	282	286	568
Rhinoconjunctivitis Symptoms			
Mean(SD)	2.9 (2.0)	4.2 (2.7)	3.6 (2.5)
Median	2.6	3.8	3.2
Q5% - Q95%	0.2 - 6.2	0.4 - 9.2	0.3 - 7.9
Nose Symptoms			
Mean(SD)	2.1 (1.4)	2.9 (1.8)	2.5 (1.7)
Median	1.9	2.8	2.3
Q5% - Q95%	0.2 - 4.6	0.3 - 6.0	0.2 - 5.6
Eye Symptoms			
Mean(SD)	0.8 (0.8)	1.3 (1.0)	1.1 (0.9)
Median	0.7	1.1	0.8
Q5% - Q95%	0.0 - 2.1	0.1 - 3.4	0.0 - 2.9

N=number of subjects
Source: Study GT-08 CSR Amendment 1 Table 9-1 (Appendix II, Table 2.1)

Figure 5: Study GT-08: Average daily rhinoconjunctivitis medication score



Source: Study GT-08 CSR Amendment 1 Figure 9-2

Table 7: Study GT-08: Summary of average daily rhinoconjunctivitis medication score during the pollen season

Treatment Group	75,000 SQ-T	Placebo	Overall
Number of Subjects	316	318	634
Entire Grass Pollen Season:			
N	282	286	568
Rhinoconjunctivitis Medication			
Mean (SD)	1.9 (2.3)	2.9 (3.0)	2.4 (2.7)
Median	1.0	2.2	1.5
Q5% - Q95%	0.0 - 6.6	0.0 - 8.9	0.0 - 7.7
Desloratadine (5 mg)			
Mean (SD)	1.6 (1.8)	2.3 (2.2)	1.9 (2.1)
Median	0.8	1.7	1.3
Q5% - Q95%	0.0 - 5.5	0.0 - 6.0	0.0 - 6.0
Budesonide nasal spray (32 mcg)			
Mean (SD)	0.3 (0.7)	0.6 (1.1)	0.5 (0.9)
Median	0.0	0.1	0.0
Q5% - Q95%	0.0 - 1.6	0.0 - 3.1	0.0 - 2.5
Prednisone (5 mg)			
Mean (SD)	0.0 (0.2)	0.1 (0.3)	0.0 (0.2)
Median	0.0	0.0	0.0
Q5% - Q95%	0.0 - 0.0	0.0 - 0.3	0.0 - 0.2

Source: Study GT-08 CSR Amendment 1 Table 9-2 (Appendix II, Table 2.2)

Table 8: Study GT-08: Summary of rhinoconjunctivitis medication use during the pollen season

Treatment Group	75,000 SQ-T			Placebo			Overall		
	N	(%)	T	N	(%)	T	N	(%)	T
Number of Subjects	316			318			634		
Entire Grass Pollen Season:	282			286			568		
Any Rhinoconjunctivitis Medication	191	(68)	3284	229	(80)	4278	420	(74)	7562
Desloratadine (8 mg)	186	(66)	2966	224	(78)	3957	410	(72)	6923
Budesonide nasal spray (32 mcg)	107	(38)	1186	164	(57)	1970	271	(48)	3156
Prednisone (5 mg)	13	(5)	137	21	(7)	115	34	(6)	252

N=number of subjects, %=percent of subjects, T=total number of days with use of rescue medication by all subjects
Source: Study GT-08 Amendment 1 Table 9-3 (EOT Table 2.6)

Table 9: Study GT-08: Analysis of average rhinoconjunctivitis symptom and medication score during the pollen season (FAS)

Treatment Group	Adjusted Mean 75,000 SQ-T	Adjusted Mean Placebo	Difference Adjusted Mean (%)	95% CL Diff. Adjusted Mean	p-value
Rhinoconjunctivitis Symptom Score:					
Number of Subjects	282	286			
Treatment Effect	2.85	4.14	-1.29(-31%)	[-1.68 ; -0.90]	<0.0001
Rhinoconjunctivitis Medication Score:					
Number of Subjects	282	286			
Treatment Effect	1.65	2.68	-1.03(-39%)	[-1.44 ; -0.63]	<0.0001

CL = confidence limits, % = Percent reduction in the 75,000 SQ-T group compared to placebo.
The comparison of the 2 treatment groups was done via an ANOVA with average rhinoconjunctivitis symptom score or average rhinoconjunctivitis medication score as response variable and treatment group as a fixed effect and pollen region as a random effect as well as adjusting for different error variation for each treatment group.
Source: Study GT-08 Amendment 1 Table 9-4 (Appendix II, Table 2.10)

The analysis of average rhinoconjunctivitis symptom scores showed that the ALK Grass tablet 75,000 SQ-T provided a reduction of the rhinoconjunctivitis symptoms of 31% when compared to placebo ($p < 0.0001$). In the peak pollen season a reduction of the rhinoconjunctivitis symptoms of 28% when compared to placebo ($p < 0.0001$) was found. The analysis of rhinoconjunctivitis medication score showed that the ALK Grass tablet 75,000 SQ-T reduced the use of rescue medication by 39% when compared to placebo ($p < 0.0001$). In the peak pollen season a reduction of 39% was found ($p < 0.0001$) when the ALK Grass tablet was compared with placebo.

7.1.1.13. Results for other efficacy outcomes

Results for Year 1 (2005)

Table 10: Study GT-08: Summary of primary and secondary outcomes; Year 1

Endpoint (FAS)	75,000 SQ-T	Placebo (mean)	p-value	Reduction*
Rhinoconjunctivitis symptom score	2.85	4.14	<0.0001	31%
Rhinoconjunctivitis symptom score (peak pollen season)	3.81	5.27	<0.0001	28%
Rhinoconjunctivitis medication score	1.65	2.68	<0.0001	39%
Rhinoconjunctivitis medication score (peak pollen season)	2.12	3.46	<0.0001	39%
Percentage well days	45%	33%	<0.0001	38%
Percentage well days (peak pollen season)	33%	22%	<0.0001	46%
Rhinoconjunctivitis symptom VAS score	15	21	<0.0001	31%
Rhinoconjunctivitis symptom VAS score (peak pollen	19	28	<0.0001	31%
RQLQ score (i.e. rhinoconjunctivitis quality of life)	1.03	1.40	<0.0001	26%
Global evaluation of rhinoconjunctivitis symptoms	7.09	8.95	<0.0001	21%
Global improvement of rhinoconjunctivitis symptoms	0.82	0.55	<0.0001	49%
Excellent rhinoconjunctivitis control	0.401	0.241	<0.0001	66%

FAS=full analysis set, VAS=visual analogue scale, RQLQ=rhinoconjunctivitis quality of life questionnaire,
*Reduction = (Active –Placebo) ÷ Placebo × 100
Source: Study GT-08 CSR Amendment 1 Table 9-17

Details of the results for the key secondary efficacy outcomes were provided.

Results for Year 2 (2006)

The trial was amended in order to extend the treatment to a total of 3 years of treatment (until the end of the grass pollen season 2007) with an additional 2 years of follow-up (after the end of each grass pollen season 2008 and 2009) to investigate long-term and sustained efficacy and safety of Grazax. At the end of the grass pollen season 2005, the participating subjects were offered to continue treatment for additionally 2 years.

All individual nose and eye symptoms showed statistically significant improvements in the Grazax group relative to placebo of 32% to 51% (all p-values ≤ 0.001) during the entire grass pollen season. Similar results were found for the peak grass pollen season (differences of 30 to 50%; all p-values ≤ 0.002).

The comparison to the symptom scores and medication use reported by the same subjects in the grass pollen season 2005 showed that the difference in treatment effect between the two grass pollen seasons was not statistically significant (p = 0.95 and p = 0.27 respectively).

A number of new outcomes were introduced in Year 2. These included:

- Combined scores: the first combined score was a simple sum of the daily symptom and medication score, while the second combined score was the daily symptom score relative to the maximum possible symptom score divided with 1 minus the medication score relative to the maximum medication score
- Super well days: a day where the subject did not need any rescue medication and did not have symptoms at all
- Asthma scores: asthma symptom scores and asthma medication scores are presented for the whole population as well as for the subgroup of subjects that had asthma at inclusion (asthma cohort, n = 70) and for the group without asthma at inclusion (n = 246)

The data set was too limited to draw any conclusions regarding the development of asthma in the two groups.

Table 11: Study GT-08: Analysis of average rhinoconjunctivitis symptom and medication score during the entire grass pollen season 2006 (FAS) and comparison to 2005 (extension cohort)

Treatment Group	Adjusted Mean Placebo	Adjusted Mean Grazax	Difference Adjusted Mean (%)	95% CL Diff. Adjusted Mean	p-value
Rhinoconjunctivitis Symptom Score 2006					
Number of Subjects	144	172			
Treatment Effect	3.76	2.40	1.36 (36%)	[0.86; 1.86]	<0.0001
Difference in Treatment Effect (2005-2006)					0.9496
Rhinoconjunctivitis Medication Score 2006					
Number of Subjects	144	172			
Treatment Effect	3.19	1.74	1.45	[0.75; 2.16]	<0.0001
Difference in Treatment Effect (2005-2006)					0.2668

CL = confidence limits, % = Percent reduction in the Grazax group relative to placebo. The comparison of the 2 treatment groups was done via an ANOVA with the average rhinoconjunctivitis symptom score or the average rhinoconjunctivitis medication score as response variable, treatment group as a fixed effect and pollen region as a random effect as well as adjusting for different error variation for each treatment group. The comparisons of the difference in treatment effect between years 2005 and 2006 were done via an ANOVA with the efficacy parameter as response variable and treatment, year and a treatment*year interaction as fixed effects. Pollen region was included as a random effect as well as adjusting for different error variation for each treatment group within year.
Source: Study GT-08 CSR Year 2 panel 9-6 (Tables 4.1.1 and 5.1)

Table 12: Overview of Efficacy Results in Year 1 (2005) (FAS) and Year 2 (2006) (FAS)

Endpoint	Grass Pollen Season 2005			Grass Pollen Season 2006		
	Placebo	Grazax	Difference	Placebo	Grazax	Difference
Primary endpoint						
Rhinoconjunctivitis symptom score	4.14	2.85	31%	3.76	2.40	36%
Rhinoconjunctivitis symptom score (peak pollen season)	5.27	3.81	28%	4.69	3.09	34%
Rhinoconjunctivitis medication score	2.68	1.65	39%	3.19	1.74	46%
Rhinoconjunctivitis medication score (peak pollen season)	3.46	2.12	39%	3.77	2.09	45%
Combined Score 1				6.94	4.10	41%
Combined Score 1 (peak pollen season)				8.44	5.14	39%
Combined Score 2				0.26	0.15	41%
Combined Score 2 (peak pollen season)				0.34	0.20	40%
Secondary endpoint						
Percentage well days	33%	45%	-38%	33%	50%	-48%
Percentage well days (peak pollen season)	22%	33%	-46%	26%	41%	-58%
Percentage super well days				32%	46%	-45%
Percentage super well days (peak pollen season)				24%	38%	-55%
Rhinoconjunctivitis symptom VAS score	21	15	31%	26.55	21.28	20%
Rhinoconjunctivitis symptom VAS score (peak pollen season)	28	19	31%	29.99	23.05	23%
RQLQ score	1.40	1.03	26%	1.26	0.85	33%
Global evaluation of rhinoconjunctivitis symptoms	8.95	7.09	21%	8.35	5.78	31%
Global improvement of rhinoconjunctivitis symptoms	0.55	0.82	-49%	0.56	0.69	-22%
Asthma symptom score				0.24	0.17	30% (ns)
Asthma symptom score (peak pollen season)				0.31	0.20	35% (ns)
Asthma medication score				0.09	0.07	24% (ns)
Asthma medication score (peak pollen season)				0.07	0.09	-29% (ns)
Excellent rhinoconjunctivitis control	0.241	0.401	-66%	0.285	0.471	-65%

FAS=full analysis set; VAS=visual analogue scale; RQLQ=rhinoconjunctivitis quality of life questionnaire; Difference=[(Placebo-Active) /Placebo] × 100; all differences were statistically significant unless marked ns: non significant
Source: Study GT-08 Year 2 CSR Panel 9-35

Results for Year 3 (2007)

The average rhinoconjunctivitis symptom and medication scores were calculated for each subject as the average of the observed total daily scores throughout the entire grass pollen season 2007. Compared to Placebo, Grazax treated subjects had a 29% reduction in average daily rhinoconjunctivitis symptom score with a reduction in both nose symptoms and eye symptoms over the entire grass pollen season 2007.

- Combined score 1: The average of symptom score and medication score.
- Combined score 2: The sum of symptom score and medication score (both normalised to a range from 0-3) divided by 2.
- Combined score 3: Symptom score relative to the maximum possible symptom score divided with 1 minus the medication score relative to the maximum medication score.
- Combined score 4: A weighted symptom score, where the observed symptom score was adjusted according to the weighting scheme presented in the SAP and a specified mathematical description.

Table 13: Study GT-08: Analysis of average daily rhinoconjunctivitis symptom and medication scores entire grass pollen season 2007

Symptom Score Grass Pollen Season 2007	N	Adjusted mean (SD)	Difference in Adjusted mean [95% CL]	Relative Difference (Difference/Placebo) x 100%	P-value
Entire Season					
Placebo	127	3.59 (0.22)	1.04 [0.52;1.56]	28.86%	0.0001
Grazax	160	2.56 (0.18)			

Source: Study GT-08 CSR Year 3 Panel 19 (Table 3.1)

Medication Score Grass Pollen Season 2007	N	Adjusted mean (SD)	Difference in Adjusted mean [95% CL]	Relative Difference (Difference/Placebo) x 100%	P-value
Entire Season					
Placebo	127	3.04 (0.48)	1.22 [0.52;1.92]	40.09%	0.0007
Grazax	160	1.82 (0.44)			

Source: Study GT-08 CSR Year 3 Panel 23 (Table 3.2)

Table 14: Study GT-08: Efficacy overview of endpoint analysis results third year of treatment

Endpoint	Grass Pollen Season 2007 (FAS)		
	Placebo	Grazax	Difference
Primary Efficacy Endpoints			
Rhinoconjunctivitis symptom score	3.59	2.56	29%
Rhinoconjunctivitis medication score	3.04	1.82	40%
Key Secondary Efficacy Endpoints			
Secondary Efficacy Endpoints			
Rhinoconjunctivitis symptom score (peak pollen season)	4.98	3.40	32%
Rhinoconjunctivitis medication score (peak pollen season)	4.15	2.22	47%
Combined Score 1	3.32	2.20	34%
Combined Score 2	0.43	0.29	32%
Combined Score 3	0.26	0.17	36%
Combined Score 4	4.21	2.94	30%
Asthma symptom score	1.19	0.82	(ns)
Asthma symptom score (peak pollen season)	1.34	0.98	(ns)
Asthma medication score	0.52	0.19	(ns)
Rhinoconjunctivitis nose symptoms (except blocked nose)	2.42	1.85	24%
Rhinoconjunctivitis eye Symptoms	1.16	0.70	40%
Percentage well days (peak pollen season)	21.41	32.15	-50%
Percentage symptom and medication free days	24.05	34.08	-42%
Percentage symptom and medication free days (peak pollen season)	16.61	24.70	-49%
Rhinoconjunctivitis VAS score	17.74	12.25	31%
Rhinoconjunctivitis VAS score (peak pollen season)	24.14	16.39	32%
Weekly overall RQLQ score (peak pollen season)	1.49	1.02	32%
Global evaluation of rhinoconjunctivitis symptoms	7.99	6.92	13%
Global improvement of rhinoconjunctivitis symptoms	0.51	0.54	(ns)
Excellent rhinoconjunctivitis control defined by >50% well days	0.24	0.43	75%
Excellent rhinoconjunctivitis control defined by >50% symptom and medication free days	0.17	0.32	88%

All analyses were based on scores in the entire grass pollen season 2007 unless otherwise specified. The primary endpoints are in bold.
FAS=full analysis set; VAS=visual analogue scale; RQLQ=rhinoconjunctivitis quality of life questionnaire. Difference = [(Placebo-Active) /Placebo] × 100; all differences were statistically significant unless marked ns: non significant
Source: Study GT-08 CSR Year 3

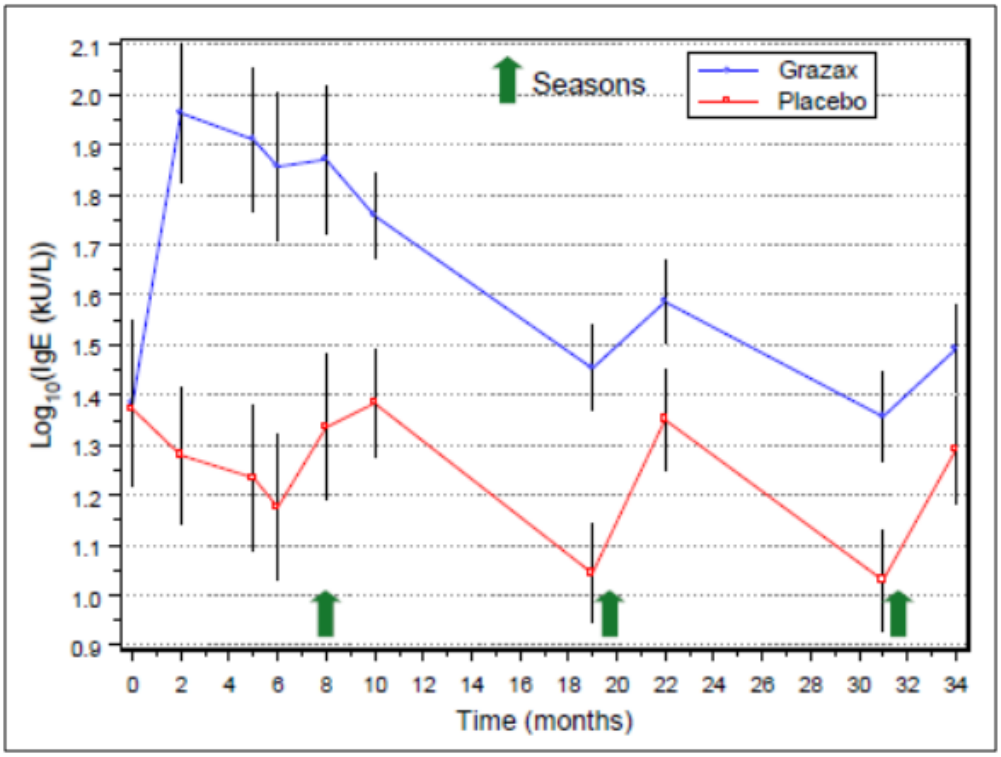
Change in Immunological Parameters Comparing Years 2005 to 2007

Changes in immunological markers were collected from subjects only at the Danish sites. The data from other sites was collected after the last grass pollen season in the final extension (Year 2009). Subject serum samples were analysed and the following *Phleum pratense* specific immunological parameters were quantified: IgE, proportion inhibited IgE (determined by the IgX assay), IgG4 and facilitated allergen presentation (FAP).

The results demonstrated:

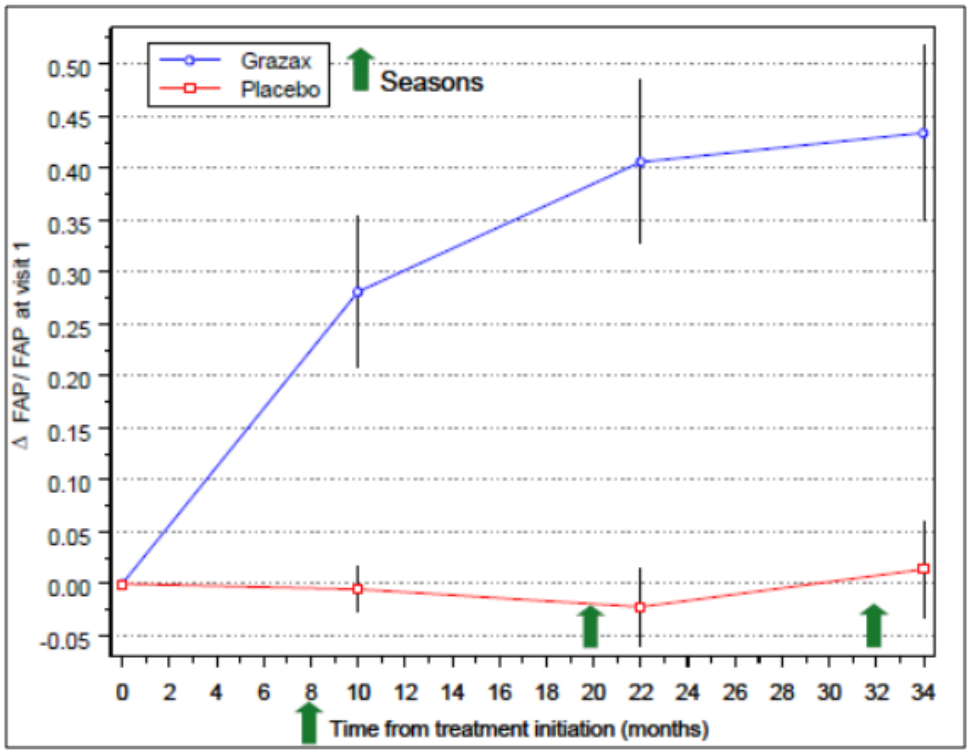
- An initial high increase in *Phleum pratense* specific IgE seen during the first 2 months of treatment. From then on the serum level of specific IgE slowly decreased in Grazax treated subjects towards the level observed for placebo, approaching each other at Visit 15 (Year 2007). For both Grazax and placebo the serum levels of specific IgE followed the pollen season with increased levels in peak seasons. At Visit 15, the change from baseline in $\log_{10}$(IgE) was no longer significantly different in the Grazax group compared to the placebo group.
- a progressive increase for *Phleum pratense* specific IgG4 antibodies over time in subjects treated with Grazax
- a progressive increase in induction of IgE specific IgE blocking antibodies competing with IgE for binding to allergen in subjects treated with Grazax
- a progressive increase in facilitated allergen presentation (FAP) over time in subjects treated with Grazax.

Figure 7: Study GT-08: Development in *Phleum pratense* specific IgE Antibodies



Blood samples analysed at visit 1= 0 months, visit 3= 2 months, visit 4= 5 months, visit 5= 6 months, visit 6= 8 months, visit 7= 10 months, visit 10= 19 months, visit 11= 22 months, visit 14= 31 months, visit 15= 34 months.
Source: Study GT-08 CSR Year 3 Panel 71

Figure 8: Study GT-08: Change in facilitated allergen presentation (FAP) from Visit 1 relative to Visit 1



Value at baseline (Visit 1) subtracted and divided with Visit 1 values. Blood samples analysed at visit 1= 0 months, visit 3= 2 months, visit 4= 5 months, visit 5= 6 months, visit 6= 8 months, visit 7= 10 months, visit 10= 19 months, visit 11= 22 months, visit 14= 31 months, visit 15= 34 months.
Source: Study GT-08 CSR Year 3 Panel 74

Results for Year 4 (2008)

First year of follow up.

Table 15: Study GT-08: Analysis average daily rhinoconjunctivitis symptom and medication scores entire grass pollen season 2008

	Placebo, adjusted mean	Grazax, adjusted mean	Difference in adjusted means (%)	95% CL Diff. adjusted means	p-value
Rhinoconjunctivitis Symptom Score, year 2008					
N with diary data	115	142			
Treatment effect	3.63	2.68	0.95 (26.2%)	[0.40; 1.50]	0.0007
Rhinoconjunctivitis Medication Score, year 2008					
N with diary data	115	142			
Treatment effect	3.25	2.32	0.93 (28.6%)	[0.14; 1.72]	0.0215

N=number of subjects, %=percent reduction in the Grazax group relative to placebo.
Source: Study GT-08 CSR Panel 9-5 Year 4 (Tables 3.1 and 3.2)

Table 16: Study GT-08: Overview of efficacy results from the grass pollen season 2008

Endpoints	Placebo	Grazax	Difference (%)	p-value
Primary Efficacy Endpoints				
Rhinoconjunctivitis symptom score	3.63	2.68	0.95 (26%)	0.0007
Rhinoconjunctivitis medication score	3.25	2.32	0.93 (29%)	0.0215
Key Secondary Efficacy Endpoints				
Quality of life assessment	1.07	0.82	0.25 (23%)	0.0041
Quality of life assessment, peak	1.66	1.19	0.47 (28%)	0.0010
Symptom and medication free days	27.63	35.22	-7.59 (-27%)	0.0384
Additional Secondary Efficacy Endpoints				
Combined score 1	3.40	2.48	0.92 (27%)	0.0014
Combined score 2	0.43	0.32	0.12 (27%)	0.0007
Combined score 3	0.27	0.18	0.09 (34%)	0.0015
Combined score 4	4.25	3.07	1.18 (28%)	0.0003
Rhinoconjunctivitis symptom score, peak	5.69	4.21	1.49 (26%)	0.0002
Rhinoconjunctivitis medication score, peak	5.10	3.67	1.43 (28%)	0.0149
Well days	38.06	49.97	-11.91 (-31%)	0.0020
Well days, peak	21.51	30.98	-9.47 (-44%)	0.0150
Symptom and medication free days, peak	15.58	21.10	-5.53 (-35%)	0.0871
Days with severe symptoms	9.27	4.80	4.46 (48%)	0.0035
Days with severe symptoms, peak	21.38	10.40	10.98 (51%)	0.0005
IgE [change from baseline in Log_{10}(IgE)]	-0.01	0.10	-0.11	0.0856
IgE-blocking factor [change from baseline]	0.07	0.21	-0.14	<0.0001
IgG_4 [change from baseline in $Log_{10}(IgG_4)$]	0.03	0.30	-0.27	<0.0001
VAS scores	18.78	12.60	6.17 (33%)	0.0007
VAS scores, peak	29.23	18.80	10.43 (36%)	0.0001
Global evaluation, most severe symptoms	8.22	6.64	1.59 (19%)	0.0021
Global evaluation, overall comparison of years	45.83	36.15	0.67*	0.1177
Rhinoconjunctivitis nose symptoms	2.49	1.89	0.60 (24%)	0.0025
Blocked nose symptoms	0.56	0.43	0.13 (24%)	0.0398
Runny nose symptoms	0.55	0.42	0.13 (23%)	0.0170
Sneezing symptoms	0.72	0.57	0.15 (21%)	0.0056
Itchy nose symptoms	0.64	0.45	0.19 (29%)	0.0010
Rhinoconjunctivitis eye symptoms	1.13	0.78	0.35 (31%)	0.0008
Gritty eye symptoms	0.70	0.53	0.17 (25%)	0.0038
Watery eye symptoms	0.42	0.25	0.17 (41%)	0.0006
Excellent rhinoconjunctivitis control	34.0	53.1	2.20*	0.0031
Number of sensitivities	4.70	3.97	0.84*	0.3767
Asthma symptom score, AaI	1.34	0.63	0.71 (53%)	0.1229
Asthma symptom score, peak, AaI	1.84	0.84	1.00 (54%)	0.1044
Asthma medication score, AaI	0.38	0.41	-0.03 (-8%)	0.8920
Asthma medication score, peak, AaI	0.56	0.40	0.16 (29%)	0.5096
Asthma prevention (% days with asthma symptoms)	21.45	14.93	0.64 *,#	0.6094
Days to first use of rescue medication (by 50%)	6	10	-4	
Days to first use of nasal steroids (by 50%)	25	NA¤	NA¤	
Days to first severe symptoms (by 50%)	14	32	-18	

The endpoints cover the FAS 2008 during the entire grass pollen season 2008 unless otherwise mentioned, %: percentages difference relative to placebo, *: odds ratio; Grazax versus placebo, peak: refers to the peak grass pollen season 2008, AaI: refers to the subpopulation with asthma at inclusion, #: odds for having a day without asthma symptoms, ¤: less than 50% in the Grazax group used nasal steroid during the entire grass pollen season of on average 65 days.
Source: Study GT-08 CSR Year 4 Panel 9-48

Results for Year 5 (2009)

Second year of follow up.

Table 17: Study GT-08: Analysis average daily rhinoconjunctivitis symptom and medication scores entire grass pollen season 2009

	Placebo, adjusted mean	Grazax, adjusted mean	Difference in adjusted means (%)	95% CL Diff. adjusted means	p-value
Rhinoconjunctivitis Symptom Score, year 2009					
N with diary data	104	137			
Treatment effect	3.4	2.56	0.84 (24.8%)	[0.28; 1.41]	0.0037
Rhinoconjunctivitis Medication Score, year 2009					
N with diary data	104	137			
Treatment effect	3.04	2.42	0.62 (20.3%)	[-0.15; 1.38]	0.1136

N=number of subjects, %=percent reduction in the Grazax group relative to placebo, CL=confidence limits.
Source: Study GT-08 CSR Year 5 Panel 9.5 (Tables 3.1 and 3.2)

The analysis of average rhinoconjunctivitis symptom scores showed that 2 years after completion of 3 years of treatment, the Grazax group had a reduction of the rhinoconjunctivitis symptom score of 25% during the entire grass pollen season when compared to placebo. This difference was statistically significant (p = 0.0037).

The analysis of rhinoconjunctivitis medication score showed that, 2 years after the end of 3 years of treatment, the Grazax group had a slightly reduced use of rhinoconjunctivitis symptomatic medications of 20% during the entire grass pollen season when compared to placebo. However, this difference was not statistically significant (p = 0.1136).

Table 18: Study GT-08: Overview of efficacy results, grass pollen season 2009

Endpoints	Placebo	Grazax	Difference (%)	p-value
Primary Efficacy Endpoints				
Rhinoconjunctivitis symptom score	3.40	2.56	0.84 (25%)	0.0037
Rhinoconjunctivitis medication score	3.04	2.42	0.62 (20%)	0.1136
Key Secondary Efficacy Endpoints				
Overall RQLQ assessment	0.85	0.69	0.16 (19%)	0.0587
Symptom and medication free days	28.04	33.53	-5.49 (-20%)	0.1737
Additional Secondary Efficacy Endpoints				
Combined score 0	6.42	4.96	1.46 (23%)	0.0128
Combined score 1	3.21	2.48	0.73 (23%)	0.0128
Combined score 2	0.41	0.31	0.10 (23%)	0.0062
Combined score 3	0.23	0.17	0.06 (27%)	0.0031
Combined score 4	4.29	3.16	1.13 (26%)	0.0026
Rhinoconjunctivitis symptom score, peak	4.94	3.60	1.34 (27%)	0.0004
Rhinoconjunctivitis medication score, peak	4.41	3.59	0.82 (19%)	0.1294
Overall RQLQ assessment, peak	1.42	1.06	0.36 (25%)	0.0081
RQLQ, activity limitation	1.14	0.98	0.16 (14%)	0.1666
RQLQ, sleep problems	0.66	0.47	0.19 (29%)	0.0309
RQLQ, non-nose/eye-symptoms	0.71	0.58	0.13 (18%)	0.1531
RQLQ, practical problems	1.10	0.96	0.14 (13%)	0.2181
RQLQ, nasal symptoms	1.13	0.97	0.16 (14%)	0.1204
RQLQ, eye symptoms	0.96	0.68	0.28 (29%)	0.0059
RQLQ, emotional function	0.55	0.48	0.07 (12%)	0.4247
RQLQ, activity limitation, peak	1.93	1.47	0.45 (24%)	0.0155
RQLQ, sleep problems, peak	1.04	0.68	0.36 (35%)	0.0199
RQLQ, non-nose/eye-symptoms, peak	1.10	0.79	0.32 (29%)	0.0251
RQLQ, practical problems, peak	1.87	1.52	0.35 (19%)	0.0631
RQLQ, nasal symptoms, peak	1.73	1.42	0.31 (18%)	0.0385
RQLQ, eye symptoms, peak	1.73	1.07	0.66 (38%)	0.0001
RQLQ, emotional function, peak	0.84	0.72	0.12 (14%)	0.3622
Well days	39.99	49.73	-9.74 (-24%)	0.0203
Well days, peak	25.47	34.78	-9.31 (-37%)	0.0356
Symptom and medication free days, peak	16.09	21.47	-5.38 (-33%)	0.1671
Days with severe symptoms	7.41	3.31	4.10 (55%)	0.0068
Days with severe symptoms, peak	17.02	6.13	10.89 (64%)	0.0002
IgE [change from baseline in Log10(IgE)]	-0.09	-0.01	-0.08	0.0389
IgE-blocking factor [change from baseline]	0.00	0.09	-0.09	<0.0001
IgG4 [change from baseline in Log10(IgG4)]	-0.04	0.31	-0.35	<0.0001
VAS scores	16.78	12.24	4.54 (27%)	0.0132
VAS scores, peak	25.11	17.06	8.06 (32%)	0.0014
Global evaluation, most severe symptoms	8.40	7.24	1.16 (14%)	0.0304
Global evaluation, overall comparison of years	58.65	44.14	0.56*	0.0256
Rhinoconjunctivitis nose symptoms	2.35	1.81	0.54 (23%)	0.0082
Blocked nose symptoms	0.51	0.43	0.08 (16%)	0.2336
Runny nose symptoms	0.50	0.38	0.12 (23%)	0.0408
Sneezing symptoms	0.72	0.55	0.17 (24%)	0.0025
Itchy nose symptoms	0.62	0.44	0.17 (28%)	0.0057
Rhinoconjunctivitis nose symptoms, peak	3.30	2.49	0.81 (25%)	0.0019
Blocked nose symptoms, peak	0.72	0.54	0.18 (25%)	0.0365
Runny nose symptoms, peak	0.76	0.56	0.20 (27%)	0.0098
Sneezing symptoms, peak	0.96	0.75	0.21 (22%)	0.0028
Itchy nose symptoms, peak	0.85	0.64	0.22 (26%)	0.0044
Rhinoconjunctivitis eye symptoms	1.04	0.73	0.31 (29%)	0.0045
Gritty eye symptoms	0.67	0.50	0.17 (26%)	0.0056
Watery eye symptoms	0.37	0.24	0.13 (36%)	0.0119
Rhinoconjunctivitis eye symptoms, peak	1.60	1.07	0.53 (33%)	0.0005

Table 18(continued): Study GT-08: Overview of efficacy results, grass pollen season 2009

Endpoints	Placebo	Grazax	Difference (%)	p-value
Gritty eye symptoms, peak	1.02	0.69	0.32 (32%)	0.0002
Watery eye symptoms, peak	0.59	0.38	0.21 (36%)	0.0074
Excellent rhinoconjunctivitis control	35.0	49.5	1.82*	0.0280
Number of sensitivities	3.88	3.43	0.88*	0.5841
Asthma symptom score, AaI	1.22	0.59	0.63 (52%)	0.1630
Asthma symptom score, peak, AaI	1.51	0.51	1.00 (66%)	0.0607
Asthma medication score, AaI	0.80	0.85	-0.05 (-7%)	0.9074
Asthma medication score, peak, AaI	1.05	0.97	0.08 (8%)	0.8898
Asthma symptom & medication free days, AaI	60.18	72.35	-12.17 (-20%)	0.2667
Asthma symptom & medication free days, peak, AaI	51.45	74.35	-22.89 (-44%)	0.0739
Odds, asthma symptom & medication free day	97.19	98.25	1.63*,#	0.4507
Odds, asthma symptom & medication free day, peak	93.18	96.74	2.17*,#	0.2167
Days to first use of symptomatic medications	6	15	-9	
Days to first use of nasal steroids	29	NA	NA	
Days to first severe symptoms	21	69	-48	
SF-36: physical health	54.54	55.29	-0.75 (-1%)	0.3586
SF-36: mental health	50.80	52.03	-1.23 (-2%)	0.2756
EQ-5D full health (per record)	95.78	97.53	1.74*	0.2421
EQ-5D full health (per subject over entire season)	61%	72%	11% (18%)	0.08

The endpoints (adjusted means) cover the FAS 2009 during the entire grass pollen season 2009 unless otherwise mentioned, %: percentages difference relative to placebo, *: odds ratio; Grazax versus placebo, peak: refers to the peak grass pollen season 2009, AaI: refers to the subpopulation of FAS 2009 with asthma at inclusion, #: for subjects in FAS 2009 without asthma at inclusion, ¤: by 50% of the subjects; note that less than 50% in the Grazax group used nasal steroid during the entire grass pollen season 2009.
Source: Study GT-08 CSR Year 5 Panel 9-62

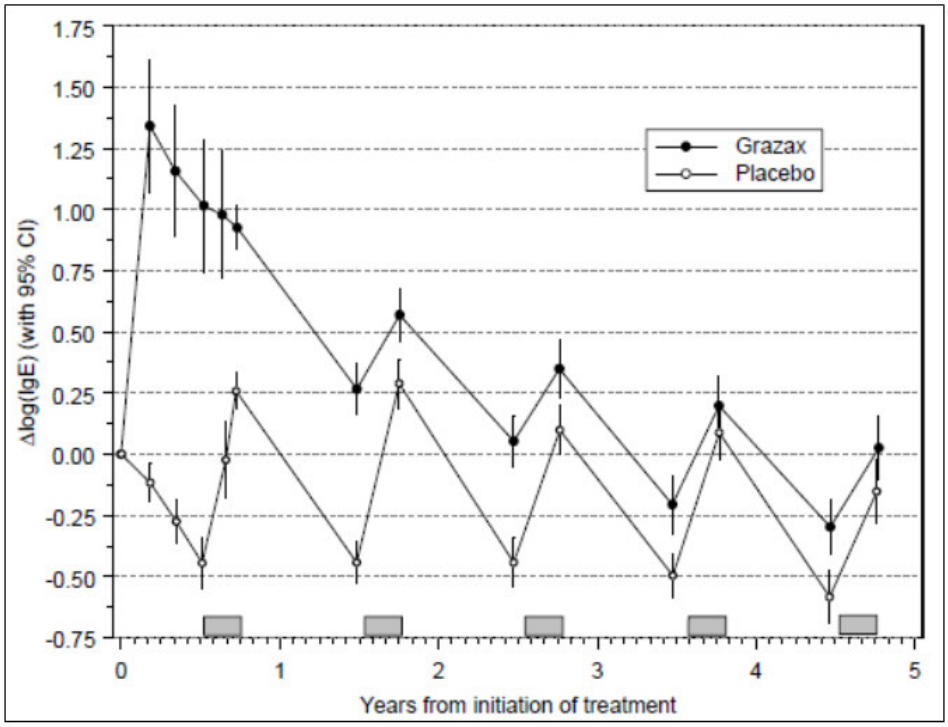
7.1.1.14. Immunological results

All serum samples were analysed after the end of the trial. For the Visits 3 to 6, serum samples were only available from the Danish subjects, whereas the remaining visits include the full population at the time of the blood sampling.

Specific IgE

Season dependency in the level of specific IgE is seen for both the Grazax and the placebo group for all years. After a marked rise in specific IgE at treatment initiation in the Grazax group, the difference between the groups decreased during the trial period. The increase in specific IgE during each grass pollen season is a well-known phenomenon, caused by a boost in natural antibody production due to the seasonal grass pollen exposure.

Figure 9: Study GT-08: Change from Baseline in Specific IgE



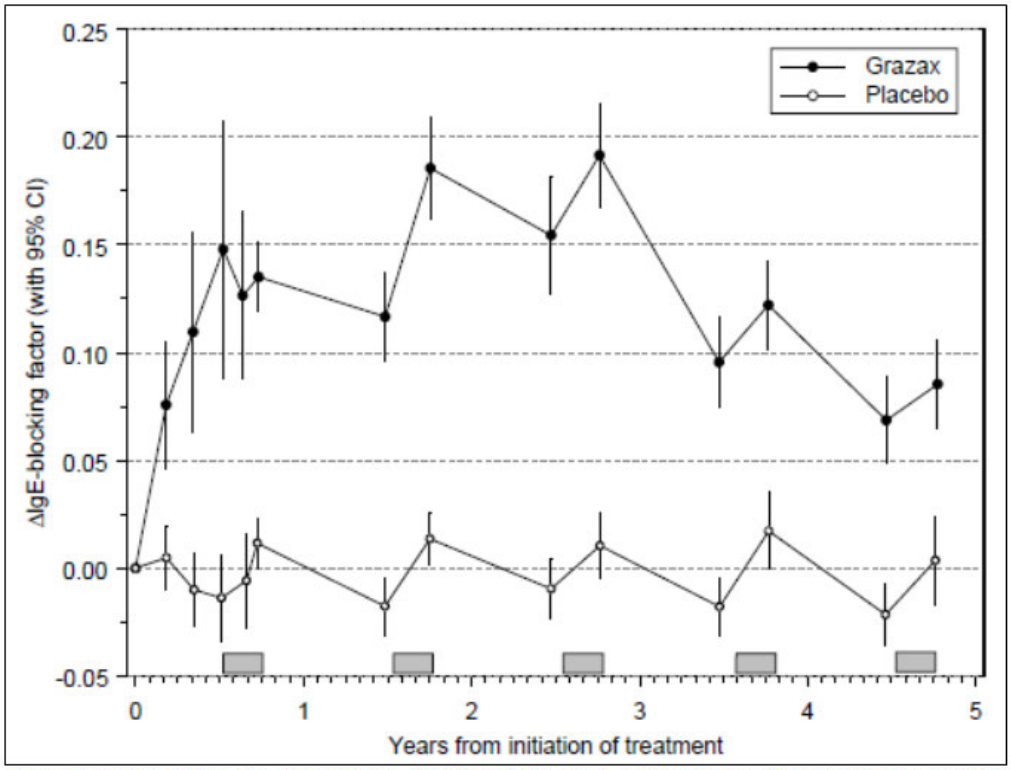
The grey boxes mark the approximate duration of the grass pollen seasons. Treatment was completed approximately 3 years after initiation.
Source: Study GT-08 Year 5 Panel 9-19 (Figure 28)

There was a statistically significant difference in specific IgE between Grazax and placebo when looking at the change from baseline and until the end of the grass pollen season 2009 (difference = -0.08, p = 0.0389). There was no change between the treatment groups when looking at the change from the end of season 2007 (that is end of treatment) and the end of season 2009 (that is end of trial) (p = 0.9495).

IgE-blocking factor

A significant increase in IgE-blocking factor in the Grazax group as compared to the placebo group was evident already after 2 months of treatment. The difference in levels of IgE-blocking factor remained present after the end of treatment.

Figure 10: Study GT-08: Change from baseline in IgE-blocking factor



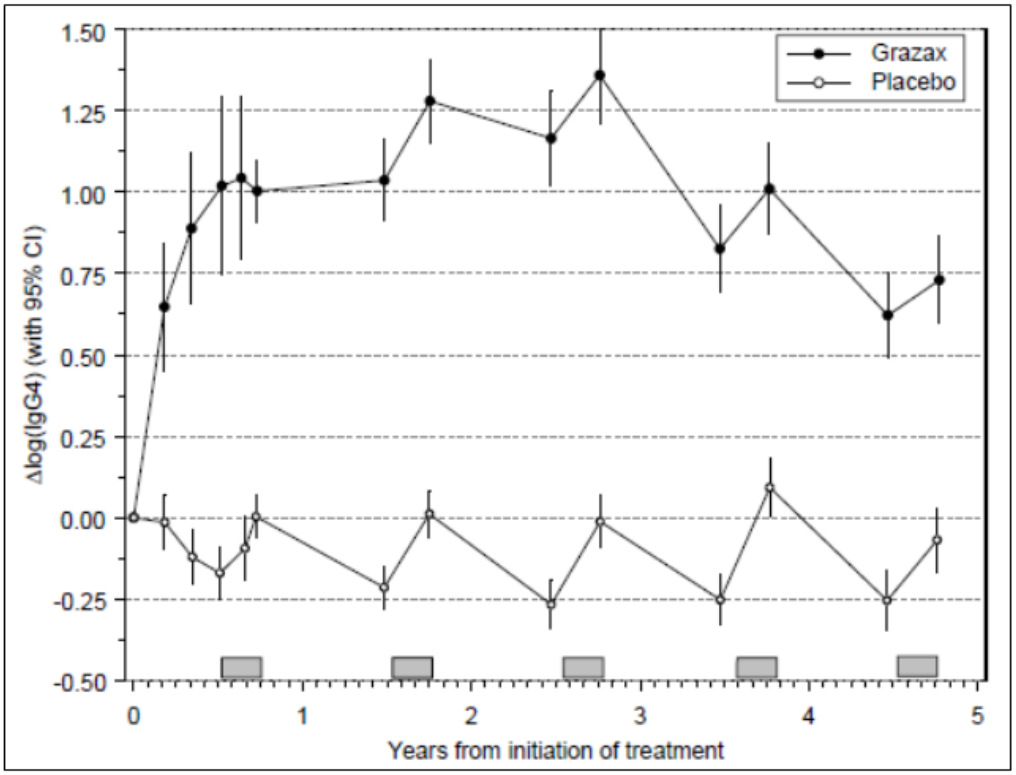
The grey boxes mark the approximate duration of the grass pollen seasons. Treatment was completed approximately 3 years after initiation.
Source: Study GT-08 Year 5 Panel 9-21 (Figure 30)

At the end of the grass pollen season 2009, the change from baseline in the Grazax group was significantly higher than the change from baseline in the placebo group (difference -0.09, $p < 0.0001$).

Specific IgG4

A significant increase in IgG4 in the Grazax group as compared to the placebo group was evident after 2 months of treatment. The increased level of IgG4 remained present after the completion of treatment.

Figure 11: Study GT-08: Change from baseline in specific IgG4



The grey boxes mark the approximate duration of the grass pollen seasons. Treatment was completed approximately 3 years after initiation.
Source: Study GT-08 Year 5 Panel 9-23 (Figure 32)

The change from baseline to the end of the grass pollen season 2009 in specific IgG4 was significantly higher in the Grazax group than in the placebo group (difference = -0.35, $p < 0.0001$).

7.1.2. Study GT-14

A Phase III Trial assessing the efficacy and safety of Grazax in subjects with seasonal grass pollen induced rhinoconjunctivitis with or without asthma.

7.1.2.1. Study design, objectives, locations and dates

A randomised, double blind, parallel group, placebo controlled trial conducted at 28 sites in the USA from December 2006 to August 2007.

Primary Objective

To evaluate the efficacy of specific immunotherapy with Grazax compared with placebo during the entire grass pollen season based on the rhinoconjunctivitis symptom score.

Secondary Objectives

To evaluate the efficacy and safety of specific immunotherapy with Grazax compared to placebo based on:

- Rhinoconjunctivitis medication score in the entire grass pollen season
- Rhinoconjunctivitis symptom and medication score in the peak grass pollen season
- Rhinoconjuctivitis symptoms assessed by VAS
- Asthma symptoms and medication score
- QoL in the grass pollen season

- Number of well days in the grass pollen season
- Global evaluation of treatment efficacy
- Safety assessments (AEs, PE, Vital signs, FEV1, laboratory assessments)
- Immunological assessments.

Treatment duration was at least 8 to 16 weeks pre-seasonal treatment and continuous treatment throughout the grass pollen season 2007.

7.1.2.2. Inclusion and exclusion criteria

Inclusion

Healthy male and female (non-childbearing potential) subjects, 18 to 65 years of age, with a clinical history of grass pollen induced allergic rhinoconjunctivitis of at least two years requiring treatment during the grass pollen season; with a clinical history of significant rhinoconjunctivitis symptoms (interfering with usual daily activities or sleep), which remain troublesome despite treatment with anti-allergic drugs during the grass pollen season; with positive skin prick test (SPT) response (wheal diameter ≥ 5 mm larger than the negative control with a flare) to *Phleum pratense* and with positive specific IgE against *Phleum pratense* (≥ IgE class 2).

Exclusion

FEV1 < 70%, a clinical history of symptomatic seasonal allergic rhinitis and/or asthma due to another allergen during, or potentially overlapping, the grass pollen season; a clinical history of significant symptomatic perennial rhinitis or allergic rhinitis/asthma caused by an allergen to which the subject is regularly exposed; a clinical history of significant recurrent acute sinusitis (defined as 2 radiologically proven episodes per year for the last two years all of which required antibiotic treatment) or chronic sinusitis; a clinical history of severe asthma (Step 4, according to GINA definition) or history of emergency visit or admission for asthma in the previous 12 months; current symptoms of, or treatment for, upper respiratory tract infection, acute sinusitis, acute otitis media or other relevant infectious process.

7.1.2.3. Study treatments

Subjects were randomised to a once daily dose of Grazax (75,000 SQ-T) or corresponding placebo. The tablet was taken with same instruction as in Study GT-08.

Rescue medication

The rescue medication was provided to subjects as predefined, open labelled medication in a step wise fashion depending on the persistency and severity and the type of symptoms and was used in addition to the investigational medicinal product to which the subjects were randomised.

Table 19: Study GT-14; rescue medication

RHINOCONJUNCTIVITIS				
Step	**Rescue medication**	**Subject dosage instructions**	**Requirements for start of use**	**Dispensed at**
1	Desloratadine tablets, 5 mg	1 tablet once daily as needed for control of allergic rhinitis	Total symptom score of ≥ 6 and start of pollen season.	Visit 4
2	Olopatadine eye drops, 1 mg/ml	1 drop in the affected eye(s) twice daily, morning and evening as needed in case of persisting allergic symptoms of the eye.	In addition to desloratadine for control of persisting eye symptoms. If symptom score was ≥ 6 or if specific eye symptom score was	Visit 4
ASTHMA				
Step	**Rescue medication**	**Subject dosage instructions**	**Requirements for start of use**	**Dispensed at**
A	Albuterol inhalation powder, 120 µg/dose	As needed 2 inhalations up to 4 times daily for relief of asthma symptoms	Asthmatics: Use as needed New asthmatics: at the investigator's discretion.	Asthmatics: Visit 4 New asthmatics: Unscheduled visit
B	Fluticasone inhalation powder, 250 µg/dose	1-2 inhalations up to twice daily for persistence of asthma symptoms.	Four or more albuterol inhalations/day for two days – or nocturnal asthma – or shortness of breath. Use in addition to albuterol.	Unscheduled visit

Step 1: Desloratadine tablets 5 mg was dispensed to the subject at Visit 4 but was not to be used before the investigator had confirmed that in his/her opinion the pollen season had started and the subject had an adequate level of symptoms (total symptom score ≥ 6).

Step 2: Olopatadine eye drops 1 mg/ml was dispensed to the subject at Visit 4 but were only to be used in addition to desloratadine tablets if eye symptoms persisted in spite of desloratadine treatment.

Once symptoms were improved the subjects were to reduce or stop use of rescue medication.

7.1.2.4. Efficacy variables and outcomes

The primary efficacy outcome was the average rhinoconjunctivitis symptom score during the entire grass pollen season calculated for each subject as the sum of the individual daily rhinoconjunctivitis symptom scores during the entire grass pollen season, divided by the number of rhinoconjunctivitis symptoms dairy recordings during the entire grass pollen season.

Other efficacy outcomes included:

- Rhinoconjunctivitis symptom score; same as for Study GT-08.
- Rhinoconjunctivitis medication score (Table 20).

Table 20: Study GT-14 Rhinoconjunctivitis medication score

Rhinoconjunctivitis Medication Step		Score/Dose [A]	Max. score/Day
1	Desloratadine - 5 mg/ 1 tablet daily	6 (per tablet)	6
2	Olopatadine eyedrops – 1.0 mg/ml / 1 drop in each eye, up to twice daily	1.5 (per drop)	6
	Max. daily rhinoconjunctivitis medication score		12

A Scoring scales were not seen by the subjects

- Rhinoconjunctivitis symptoms assessed by VAS
- Asthma symptom score
- Asthma medication score
- Quality of life
- Number of well days; defined as days without use of rescue medication and without symptoms
- Global evaluation

Details of evaluation methods and scales were provided.

7.1.2.5. Randomisation and blinding methods

Randomisation was performed by the trial sponsor but details were not provided in the CSR.

Double blinding of the IMP was ensured by providing placebo tablets similar to the active IMP with regards to appearance, smell and taste.

7.1.2.6. Analysis populations

- Full analysis set (FAS): All randomised subjects (ITT).
- Per protocol analysis set (PP): Subjects who did not have major protocol deviations that is subjects who: did not take prohibited medication; had sufficient trial drug compliance defined as at least 80% of drug compliance; provided sufficient diary data defined as at least 50% of diary data in the pollen season; did not have any other significant protocol deviations with influence on the primary endpoint.

7.1.2.7. Sample size

The primary efficacy endpoint was the average rhinoconjunctivitis symptom score during the entire grass pollen season. Data from the previous Grazax trial, GT-08, was used to calculate the required sample size. The mean values and standard deviations (SD) for the symptom score obtained in GT-08 were 2.4 (1.6) for Grazax and 3.4 (2.2) for placebo. The power calculation was made by simulation, assuming that the mean and SD of the symptoms scores as in the GT-08 trial but with some uncertainty (a SD of 10%) of each of the values. Based on 1,000 sample size simulations a trial design with approximately 150 subjects in each treatment group was proposed. The proposed trial design with 150 subjects per treatment group, assuming a 20% dropout rate, would be able to detect a 24% reduction in mean compared to placebo in the primary endpoint at a 5% significance level and with 90% power.

7.1.2.8. Statistical methods

All statistical tests use a significance level of 5% and all tests and confidence intervals are two-sided. The null hypothesis was the hypothesis of no difference and the alternative to the null hypothesis was the hypothesis of difference. The test of the hypothesis was done via an ANOVA with the average rhinoconjunctivitis symptom score as response variable and treatment group as a fixed effect and pollen region as a random effect as well as adjusting for different

error variation for each treatment group. The primary outcome was the difference in adjusted means between the 2 groups with 2-sided 95% confidence interval as well as the p-value. In addition, the difference in adjusted means between the two treatment groups relative to the adjusted mean of the placebo group was presented as a percentage with 2-sided 95% CI. The CI for the relative treatment difference was estimated by bootstrapping using the mean estimates. Furthermore, adjusted means for the 2 treatment groups with standard errors and 2-sided 95% CI were presented. Finally, a p-value describing the statistical significance of the pollen region was also presented. One unique pollen count station exists for each site; therefore site within pollen region was not included as a variable in the analysis. In addition to the parametric analysis, a Friedman test of the treatment difference was performed, as a control of the parametric method.

The secondary endpoints were ranked, and no statistical conclusions were made based on test of a null hypothesis that has a rank lower than or equal to the null hypothesis that was the first not to be rejected. The weekly overall RQLQ analysis was analysed using a repeated measurement ANOVA including treatment group, week and treatment by week interaction as a fixed effects, pollen area as a random effect and adjusting for subject variation. An AR(1) or compound symmetry covariance structure was applied. Pollen regions were pooled into pollen areas, due to regions with too few observations. The rhinoconjunctivitis medication score and the percentage of well days were analysed using the same method as described for the primary analysis.

7.1.2.9. Participant flow

Table 21: Study GT-14: Subject disposition (all subjects)

Treatment Group	Placebo N (%)	Grazax N (%)	Overall N (%)
Screened			405
Full Analysis Set (FAS)	166	163	329
Per protocol (PP)	119 (72%)	121 (74%)	240 (73%)
Subjects with diary data (entire grass pollen season)	150 (90%)	139 (85%)	289 (88%)
Subject with diary data (peak grass pollen season)	143 (86%)	137 (84%)	280 (85%)
Withdrawn from Trial	26 (16%)	27 (17%)	53 (16%)
Reason for Withdrawal			
Withdrawal of consent	7 (4%)	8 (5%)	15 (5%)
Lost to follow-up	5 (3%)	2 (1%)	7 (2%)
Non-compliance with protocol	3 (2%)	1 (<1%)	4 (1%)
Pregnancy	2 (1%)	- (-)	2 (<1%)
Adverse event	5 (3%)	10 (6%)	15 (5%)
Other	4 (2%)	6 (4%)	10 (3%)
Withdrawal Initiated by			
Investigator	6 (4%)	7 (4%)	13 (4%)
Sponsor	1 (<1%)	- (-)	1 (<1%)
Subject	19 (11%)	20 (12%)	39 (12%)
Completed	140 (84%)	136 (83%)	276 (84%)

9 of the subjects with data in the grass pollen season dropped out before the peak grass pollen season and thus did not provide any data in the peak grass pollen season
N= Number of subjects; %= Percent of the full analysis set (all randomised subjects)
Source: Study GT-14 CSR Panel 7-1 (Table 1.1)

7.1.2.10. Major protocol violations/deviations

Six subjects were found not to comply with the inclusion/exclusion criteria and the majority of the major deviations leading to exclusion from the PP analysis set, were due to low diary

compliance (< 50% of diary data) as a result of subjects (48) withdrawing before or during the grass pollen season.

7.1.2.11. Baseline data

The trial population comprised subjects between 18 to 65 years of age (mean 35.9 years) with a mean duration of grass pollen allergy of 21 years. The majority of subjects were White (81%) or Black/African American (13%). No major differences between treatment groups were observed.

Tabulated data was provided.

7.1.2.12. Results for the primary efficacy outcome

The primary efficacy endpoint was the average rhinoconjunctivitis symptom score during the entire grass pollen season.

The analysis of average rhinoconjunctivitis symptom scores showed no statistically significant differences between Grazax and placebo (p = 0.3475).

Table 22: Study GT-14: Summary of average daily rhinoconjunctivitis symptom score during the entire grass pollen season (FAS)

	Placebo	Grazax
Rhinoconjunctivitis Symptoms		
N	150	139
Mean (SD)	6.03 (3.68)	5.59 (3.53)
Median	5.88	5.47
Q25%-Q75%	3.46-8.41	2.83-7.77
Min-max	0.00-17.23	0.00-15.61
Nose Symptoms		
N	150	139
Mean (SD)	4.17 (2.55)	3.96 (2.39)
Median	4.06	3.81
Q25%-Q75%	2.18-5.96	2.04-5.48
Min-max	0.00-11.69	0.00-10.79
Eye Symptoms		
N	150	139
Mean (SD)	1.86 (1.33)	1.63 (1.32)
Median	1.79	1.31
Q25%-Q75%	0.70-2.73	0.60-2.39
Min-max	0.00-5.92	0.00-5.92

N= Number of subjects with diary data
Average daily symptom score is calculated from daily diary data during the entire grass pollen season. Daily score range: Rhinoconjunctivitis symptoms 0-18; Nose symptoms 0-12; Eye symptoms 0-6.
Source: Study GT-14 CSR Panel 9-3 (Table 2.1.1)

Table 23: Study GT-14: Analysis of average rhinoconjunctivitis symptom score during the entire grass pollen season (FAS)

Rhinoconjunctivitis Symptom Score		N	Estimate	SE	95% CL	p-value
Treatment Effect Adjusted means	Placebo	150	6.06	0.40	[5.25; 6.87]	0.3475
	Grazax	139	5.69	0.39	[4.90; 6.47]	
	Difference (placebo-Grazax)		0.37	0.40	[-0.41; 1.16]	
	(Difference/placebo) x 100%		6.18		[-6.83; 19.77]	

N= Number of subjects with diary data; CL= Confidence limits; SE = Standard error
Average daily rhinoconjunctivitis symptom score is calculated from daily diary data during the entire grass pollen season. The comparison of the two treatment group is done via an ANOVA with the average rhinoconjunctivitis symptom score as response variable and treatment group as fixed effect. Furthermore, pollen region is included as a random effect as well as adjusting for different error variation for each treatment group.
Source: Study Gt-14 CSR Panel 9-4 (Table 3.1.1)

7.1.2.13. Results for other efficacy outcomes

Average daily rescue medication score

The analysis of average rescue medication score showed no statistically significant differences between Grazax and placebo (p = 0.0827).

The non-parametric test of the average rhinoconjunctivitis medication score showed no differences between treatments (p = 0.2141).

Table 24: Study GT-14: Summary of average daily rescue medication score during the entire grass pollen season (FAS)

	Placebo	Grazax
Rhinoconjunctivitis Medication		
N	150	139
Mean (SD)	1.49 (2.23)	1.11 (3.53)
Median	0.29	0.22
Q25%-Q75%	0.00-2.10	0.00-1.30
Min-max	0.00-10.89	0.00-10.73
Desloratadine		
N	150	139
Mean (SD)	1.19 (1.75)	0.90 (1.48)
Median	0.23	0.14
Q25%-Q75%	0.00-1.89	0.00-1.15
Min-max	0.00-6.00	0.00-6.00
Olopatadine		
N	150	139
Mean (SD)	0.30 (0.77)	0.21 (0.61)
Median	0.00	0.00
Q25%-Q75%	0.00-0.18	0.00-0.13
Min-max	0.00-4.93	0.00-5.19

N= Number of subjects with diary data
Average daily rhinoconjunctivitis medication score is calculated from daily diary data during the entire grass pollen season. Maximum daily score: Medication score [0-12]; desloratadine [0-6]; olopatadine [0-6]
Source: Study GT-14 CSR Panel 9-6 (Table 2.4.1)

Table 25: Study GT-14: Analysis of average rescue medication score during the entire grass pollen season (FAS)

Rhinoconjunctivitis Symptom Score		N	Estimate	Std. Error	95% CL	p-value
Treatment Effect Adjusted means	Placebo	150	1.47	0.22	[1.03; 1.91]	0.0827
	Grazax	139	1.07	0.20	[0.67; 1.48]	
	Difference (placebo-Grazax)		0.40	0.23	[-0.05; 0.85]	
	(Difference/placebo) x 100%		27.12		[-10.7; 48.35]	

N= Number of subjects with diary data
CL= Confidence limits
Average daily rhinoconjunctivitis symptom score is calculated from daily diary data during the entire grass pollen season. The comparison of the two treatment group is done via an ANOVA with the average rhinoconjunctivitis symptom score as response variable and treatment group as fixed effect. Furthermore, pollen region is included as a random effect as well as adjusting for different error variation for each treatment group.
Source: Study Gt-14 CSR Panel 9-4 (Table 3.1.1)

Table 26: Study GT-14: Results for other efficacy outcomes

Endpoints	Placebo	Grazax	Difference (%)	p-value
Rhinoconjunctivitis Quality of Life score	1.44	1.36	5.33	0.5293
% of rhinoconjunctivitis well days entire GPS	26.03	27.44	5.44	0.6965
% of Rhinoconjunctivitis well days peak GPS	23.41	26.07	11.34	0.5062
Average rhinoconjunctivitis symptom score peak GPS	6.49	5.99	7.72	0.2650
Average rhinoconjunctivitis symptom score during first 7 days of GPS	6.28	5.92	5.76	0.4371
Average rhinoconjunctivitis medication score during first 7 days of GPS	1.12	0.90	19.78	0.3408
Average rhinoconjunctivitis medication score peak GPS	1.57	1.17	25.38	0.1230
Combined score entire GPS	7.53	6.74	10.41	0.1413
Combined score peak GPS	8.05	713	11.32	0.1290
Average daily VAS score entire GPS	35.85	32.23	10.10	0.1670
Average daily VAS score peak GPS	38.00	34.00	10.53	0.1536
Global evaluation (compared to previous year)	9.99	9.88	1.07	0.8361
Overall global evaluation - OR = 1.98				0.0016
Overall global evaluation – proportion improved OR = 2.24				0.0010
Excellent rhinoconjunctivitis control (%) OR = 1.36	22	27		0.2506
Rhinoconjunctivitis symptom and medication free days entire GPS	13.48	12.65	6.16	0.7492
Rhinoconjunctivitis symptom and medication free days peak GPS	11.52	11.64	0.99	0.9689
Average daily asthma symptom score entire GPS	1.56	1.68	8.06	0.7729
Average daily asthma symptom score peak GPS	1.58	2.10	32.73	0.2902
Average daily asthma medication score entire GPS	0.34	0.27	21.41	0.6141
Average daily asthma medication score peak GPS	0.30	0.43	41.92	0.5363
% asthma well days entire GPS	59.20	58.62	0.98	0.9482
% asthma well days peak GPS	55.92	54.91	1.81	0.9158

Combined score = sum of daily symptom score and daily medication score
The Global Evaluation is performed at the Screening Visit and the questions is phrased "How do you assess the severity of your rhinoconjunctivitis symptoms, when they were the most severe during the previous grass pollen season (2006) and at the end of the grass pollen season at Visit 6, where the question is phrased "How do you assess the severity of your rhinoconjunctivitis symptoms, when they were the most severe during this grass pollen season (2007)" Score range: Rhinoconjunctivitis symptoms 0-18; Nose symptoms 0-12; Eye symptoms 0-6.
The overall global evaluation was performed at the end of the grass pollen season (visit 6). The question was phrased: "Compared to your rhinoconjunctivitis symptoms in previous grass pollen seasons, how have you felt overall in this grass pollen season (2007)?" The responses are pooled as Improved. Much better or better; Not improved: the same, worse or much worse.
Excellent control = subject who had more than 50% well days during GPS
Source: Study GT-14 CSR Tables 3.7.1, 3.1.1, 3.6.1, 3.4.1, 3.5.1, 3.10.1. 3.11.1, 3.12.1, 3.13.1, 3.8.1, 3.14.1, 3.15.1, 3.16.1

Immunological Parameters

Blood samples were drawn at the screening visit (Visit 1), the pre-season visit (Visit 4) and at the end of season visit (Visit 6) to investigate the immunological parameters specific IgE and IgE blocking antibodies (measured by the IgX assay).

IgE

In the Grazax group there was an initial rise in specific IgE (from Visit 1 to Visit 4), which tended to level out over time (Visit 4 to Visit 6). For the placebo group there was only a minor variation in the level of specific IgE during the first part of the trial followed by an increase in IgE during the grass pollen season (from Visit 4 to Visit 6). The increase in IgE levels due to pollen exposure during the grass pollen season was less marked in the Grazax group compared to the increase in the placebo group. The Grazax treated group exhibited a larger change in significantly higher specific IgE values from baseline ($p < 0.0001$) than the placebo group.

Table 27: Study GT-14: Analysis of specific IgE (log_{10} transformed) (FAS)

Specific IgE	Difference between Visit	Estimated difference	SE	95% CL	p-value
Difference placebo	V4 -V1	-0.556	0.035	[-0.625; -0.487]	p<0.0001
vs. Grazax	V6 - V1	-0.334	0.035	[-0.403; -0.265]	p<0.0001

CL = confidence limits, SE = standard error
The estimates of the difference between the two treatment groups is done via a repeated measurement analysis with antibody difference from baseline as response variable, treatment group, visit and pollen region as fixed effects, baseline as covariate, and adjustment for different error variation for each treatment group. AR (1) was used as covariance pattern. Pollen regions were pooled into pollen areas. IgE was log10 transformed to get approximately normally distributed data.
Source: Study GT-14 CSR Panel 9-27 (Table 5.4)

IgG4

For the Grazax group, a constant increase in IgG4 level was observed over time. In the placebo group, no change in IgG4 was observed. The IgG4 values in the two treatment groups were about the same at treatment initiation (Visit 1). The Grazax treated group exhibited a larger change in specific IgG4 values from baseline than the placebo group.

Table 28: Study GT-14: Analysis of IgG4 (log_{10} transformed) (FAS)

IgG4	Difference between Visit	Estimated difference	SE	95% CL	p-value
Difference placebo	V4 -V1	-0.114	0.022	[-0.157; -0.071]	p<0.0001
vs. Grazax	V6 - V1	-0.172	0.022	[-0.214; -0.129]	p<0.0001

CL = confidence limits, SE = standard error
The estimates of the difference between the two treatment groups is done via a repeated measurement analysis with antibody difference from baseline as response variable, treatment group, visit and pollen region as fixed effects, baseline as covariate, and adjustment for different error variation for each treatment group. AR (1) was used as covariance pattern. Pollen regions were pooled into pollen areas. IgE was log10 transformed to get approximately normally distributed data.
Source: Study GT-14 CSR Panel 9-30 (Table 5.4)

IgE-blocking Antibodies (IgX)

For the placebo group, no difference in the fraction of IgE allowed to bind to allergen was observed over time. For the Grazax group, an almost constant decrease was observed. The IgE-blocking antibody values in the two treatment groups were virtually identical at treatment initiation (Visit 1). A significantly higher induction of IgE-blocking antibodies as compared to baseline was observed for the Grazax group than for the placebo group.

Table 29: Study GT-14: Analysis of IgE-blocking antibodies (FAS)

IgG4	Difference Between Visit	Estimated difference	SE	95% CL	p-value
Difference placebo	V4 -V1	0.095	0.014	[0.068; 0.122]	p<0.0001
vs. Grazax	V6 - V1	0.121	0.013	[0.095; 0.148]	p<0.0001

CL = Confidence Limits; SE = standard error
The estimates of the difference between the two treatment groups is done via a repeated measurement analysis with antibody difference from baseline as response variable, treatment group, visit and pollen region as fixed effects, baseline as covariate, and adjustment for different error variation for each treatment group. AR(1) was used as covariance pattern. Pollen regions were pooled into pollen areas.
Source: Study GT-14 CSR Panel 9-33 (Table 5.4)

7.2. Other efficacy studies

7.2.1. Study GT-07

A Randomised, parallel group, double blind, placebo controlled Phase II Trial assessing the safety and efficacy of ALK Grass tablet *Phleum pratense* in subjects with seasonal grass pollen induced rhinoconjunctivitis and mild to moderate grass pollen induced asthma.

Comment: Formulation used in the study was not the final formulation. The formulation was the "progressing formulation".

7.2.1.1. Study design, objectives, locations and dates

A randomised, parallel group, double blind, placebo controlled study conducted at 15 sites (11 in Denmark and 4 in Sweden) from February to September 2004.

Primary objective

To evaluate the safety of the ALK Grass tablet in a dosage of 75,000 SQ-T as compared to placebo in subjects diagnosed with mild to moderate grass pollen induced asthma as well as grass pollen induced rhinoconjunctivitis.

Secondary objective

To evaluate the efficacy of the ALK Grass tablet in a dosage of 75,000 SQ-T as compared to placebo in subjects diagnosed with mild to moderate grass pollen induced asthma as well as grass pollen induced rhinoconjunctivitis.

7.2.1.2. Study Population

Inclusion

Male or female (non-childbearing potential) subjects, 18 to 65 years of age with clinical history of significant grass pollen induced allergic rhinoconjunctivitis and mild to moderate grass pollen induced asthma of 2 years or more, a positive skin prick test and specific IgE to *Phleum pratense* (≥ CAP allergy Class 2) and a clinical history of mild to moderate grass pollen induced asthma (dyspnoea, wheeze, and cough) during the last 2 grass pollen seasons controlled by appropriate medications in accordance with GINA Guideline (2002).

Exclusion

Clinical history of significant asthma outside the grass pollen season, FEV1 < 70% predicted; perennial allergic rhinitis and/or asthma

7.2.1.3. Study treatments

Subjects were randomised to treatment with ALK grass tablet or placebo taken once daily in the morning for 12 weeks.

Rescue medication (rhinoconjunctivitis)

- Step 1 loratadine 10 mg and levocabastine eye drops (05 mg/mL, 1 drop in each eye, twice daily).
- Step 2 Budesonide nasal spray; 32 µg per actuation (as add on to Step 1)
- Step 3 Prednisone up to 50 mg orally at time of visit and up to following 2 days

7.2.1.4. Efficacy outcomes

Efficacy was a secondary objective of the trial. The efficacy endpoint was average daily rhinoconjunctivitis symptom score as well as average rhinoconjunctivitis medication score for the grass pollen season. (Outcome measures were same as for Study GT-08).

7.2.1.5. Statistical methods

No formal statistical sample size and power calculations were made. Outcome measures are described by treatment group displaying number of subjects, mean, SD, median, 5%-quantile, 95%-quantile, minimum and maximum. Difference between treatment groups in the average daily rhinoconjunctivitis symptom score as well as the average daily rhinoconjunctivitis medication score for the pollen season were post-hoc tested using the following ANOVA models:

- Model 0: Treatment as fixed effect, separate errors for each treatment group and pollen region as a random effect
- Model 1: Treatment as fixed effect and separate errors for each treatment group
- Model 2: Treatment as fixed effect and the same error for both treatment groups (equivalent to t-test)

The difference between active and placebo was estimated and tested in all 3 models and it was tested whether Model 0 could be reduced to Model 1 and whether Model 1 could be reduced to Model 2.

For rhinoconjunctivitis medication score the underlying model assumptions for the ANOVA models were not entirely fulfilled and a square root transformation of the rhinoconjunctivitis medication score variable was performed. After square root transformation the underlying assumptions were still not entirely fulfilled, and therefore a Wilcoxon Rank-sum test was also performed.

7.2.1.6. Participant flow

Table 30: Study GT-07; Subject disposition

Group	Placebo (N=40)	75.000 SQ-T (N=74)	Overall (N=114)
Screened			130
Full analysis set	40 (100%)	74 (100%)	114 (100%)
PP set	32 (80.0%)	61 (82.4%)	93 (81.6%)
Completed trial	36 (90.0%)	66 (89.2%)	102 (89.5%)
Withdrawals	4 (10.0%)	8 (10.8%)	12 (10.5%)
Reason for Withdrawal			
Adverse event	0 0	3 (4.1%)	3 (2.6%)
Subject non-compliance with protocol	0 0	1 (1.4%)	1 (<1.0%)
Lost to follow-up	1 (2.5%)	2 (2.7%)	3 (2.6%)
Other	3 (7.5%)	2 (2.7%)	5 (4.4%)

N = Number of subjects
% = Percent subjects of Full Analysis set (all randomised subjects)
Source: Study GT-07 (EOT Table 1.1)

7.2.1.7. Baseline data

The demography and baseline characteristics of all subjects were comparable for the 2 treatment groups. The subject population comprised ⅔ males and ⅓ females (a few more females and currently smoking subjects were randomised to placebo). All but 2 (Asian and Mulatto) were Caucasian and all were aged between 18 and 64 years. All had suffered from grass pollen induced asthma for 2 to 45 years, and grass pollen induced allergy for 2 to 51 years.

Tabulated data was provided.

7.2.1.8. Results for the efficacy outcome

In the ITT population, in the grass pollen season both symptom and medication score were lower for subjects treated with the ALK Grass tablet 75,000 SQ-T when compared to placebo

(average symptom score 2.27 compared to 3.04 and average medication score 2.60 compared to 3.81. Results were similar for the PP population.

Table 31: Study GT-07; Daily seasonal average medication and symptom scores

	Placebo FA set (N=39)#	75,000 SQ-T FA set (N=68)#	Placebo PP set (N=32)	75,000 SQ-T PP set (N =61)
Rhinoconjunctivitis Symptom Scores				
Mean (SD)	3.04 (2.12)	2.27 (1.86)	3.25 (2.16)	2.05 (1.66)
Median	2.66	1.90	2.87	1.77
Min - Max	0 - 7.28	0.02 - 9.50	0.11 - 7.28	0.02 - 8.14
Nose Symptoms				
Mean (SD)	2.16 (1.62)	1.52 (1.20)	2.34 (1.66)	1.39 (1.13)
Median	1.91	1.23	2.05	1.10
Min - Max	0 - 5.87	0 - 5.34	0.11 - 5.87	0 - 5.34
Eye Symptoms				
Mean (SD)	0.88 (0.68)	0.75 (0.78)	0.91 (0.64)	0.67 (0.64)
Median	0.75	0.56	0.86	0.48
Min - Max	0 - 2.6	0 - 4.5	0 - 2.26	0 - 2.91
Rhinoconjunctivitis Medication Scores				
Mean (SD)	3.81 (4.14)	2.60 (3.95)	4.17 (4.14)	2.44 (3.92)
Median	3.19	1.23	3.58	1.17
Min - Max	0 - 14.1	0 - 19.9	0 - 14.1	0 - 19.9
Loratadine tablets (10 mg)				
Mean (SD)	2.39 (2.55)	1.42 (1.75)	2.64 (1.67)	1.34 (1.67)
Median	2.00	0.92	2.74	1.15
Min - Max	0 - 9.16	0 - 7.47	0 - 9.16	0 - 7.47
Levocabastine eye drops (0.5 mg/ml)				
Mean (SD)	0.92 (1.78)	0.79 (1.72)	1.01 (1.86)	0.73 (1.73)
Median	0	0.08	0	0.08
Min - Max	0 - 7.00	0 - 8.91	0 - 7	0 - 8.91
Budesonide nasal spray (32) µg				
Mean (SD)	0.50 (0.72)	0.37 (1.04)	0.52 (0.73)	0.35 (1.05)
Median	0.10	0	0.13	0
Min - Max	0 - 2.07	0 - 6.64	0 - 2.07	0 - 6.64
Prednisone/Prednisolon tablets (5 mg)				
Mean (SD)	0 (-)	0.02 (0.17)	0	0.02 (0.18)
Median	0	0	0	0
Min - Max	0 - 0	0 - 1.39	0 - 1.39	0 - 1.39

N=number of subject; #number of subjects with seasonal diary data were 39 placebo and 68 active.
FA=full analysis; PP=per protocol analysis
The highest possible symptom score was 18 and highest possible medication score was 38.
Source: Study GT-07 CSR Table 9-2 (EOT Table 8.1a – 8.2b)

Even though the subjects suffered from moderate to severe rhinoconjunctivitis, ⅓ of the subjects still did not use medication to treat their symptoms. None of the placebo treated subjects reached the final step of rescue medication, while 4.4% of the actively treated subjects did. In contrast 59.0% of the placebo subjects reached the intermediate step (Budesonide), compared to 27.9% of the actively treated subjects, and overall a higher percentage of the actively treated subjects were able to stay on the first step of rescue medication (Loratadine tablets and Levocabastine eye drops).

Post hoc it was decided to test the observed differences in the efficacy endpoints.

As the pollen region was not statistical significant and equal variance could be accepted at a 5% significance level the Model 2 is presented.

Neither the rhinoconjunctivitis score nor the medication score were statistically significant for the full analysis set (ITT).

Table 32: Study GT-07; Analysis of average daily rhinoconjunctivitis symptom and medication score

	Placebo Adjusted mean	Active Adjusted mean	Difference in adjusted mean	P-value	Reduction*
Rhinoconjunctivitis symptom score FA set, non-transformed data					
ANOVA model 2	2.27	3.04	-0.78	0.0503	-25%
Rhinoconjunctivitis symptom score PP set, non-transformed data					
ANOVA model 2	2.05 (0.21)	3.25 (0.38)	-1.20	0.0039	-37%
Rhinoconjunctivitis medication score FA set, non-transformed data					
ANOVA model 2	3.81	2.60	-1.21	0.1355	-32%
Wilcoxon Rank Sum	NA	NA	NA	0.1955	NA
Rhinoconjunctivitis medication score PP set, non-transformed data					
ANOVA model 2	4.17	2.44	-1.73	0.0507	-41%
Wilcoxon Rank Sum	NA	NA	NA	0.0357	NA
Rhinoconjunctivitis medication score FA set, square root transformed data					
ANOVA model 2	1.51	1.19	-0.32	0.1732	NA
Rhinoconjunctivitis medication score PP set, square root transformed data					
ANOVA model 2	1.65	1.14	-0.51	0.0400	NA

SE=standard error of adjusted mean; FA set=full analysis set; NA=not available;
* $reduction = 100 \times \frac{Active - Placebo}{Placebo}$
Source: Study GT-07 CSR Table 9-4 (Section 6.6 and Appendix IX)

No immunological testing was done in this study.

7.2.2. Study P05238

A multicentre, double blind, randomised, placebo controlled, parallel group study evaluating the efficacy and safety of grass (*Phleum pratense*) sublingual tablet (SCH 697243) in adult subjects with a history of grass pollen induced rhinoconjunctivitis with or without asthma.

Comment: The formulation for SCH 697243 is not provided in the CSR. The study was conducted by Schering Plough (owned by MSD). There is a statement that Grazax is the approved tradename in the EU, while in the US, the approved tradename is Grastek. With the exception of tradename, both products are identical. The original manufacturer (ALK) has a partnership with Merck Sharp & Dohme Corp whereby Merck have the rights to develop and commercialise Grastek in the USA

7.2.2.1. Study design, objectives, locations and dates

A multicentre, double blind, randomised, placebo controlled, parallel group study conducted at 69 centres (59 in USA and 10 in Canada) from January 2008 to September 2009.

The study consisted of an observational grass pollen season, period in Year 2008 where no investigational medicinal product (IMP) was given. Open label rescue medications for the rhinoconjunctivitis and asthma symptoms were provided. In Year 2009 (the treatment period), the subjects were treated once daily with either SCH 697243 (Timothy grass allergy immunotherapy tablet [grass AIT] or placebo for approximately 16 weeks prior to the grass pollen season (GPS) and during the GPS.

Primary objective

To evaluate the efficacy of the grass sublingual tablet (SCH 697243) versus placebo in the treatment of grass pollen induced rhinoconjunctivitis based on the total combined (sum of) rhinoconjunctivitis daily symptom score (DSS) and rhinoconjunctivitis daily medication score (DMS) averaged over the entire GPS.

Secondary objectives

- To assess overall safety and compare the following between the SCH 697243 and placebo groups:

  - The average rhinoconjunctivitis DSS for the entire GPS
  - The average rhinoconjunctivitis DMS for the entire GPS
  - The average weekly rhinoconjunctivitis quality of life total score for the entire GPS
- To assess and compare the following immunological variables between the SCH 697243 and placebo groups:
  - IgE level against *Phleum pratense*
  - IgG4 level against *Phleum pratense*
  - Effect of IgE-blocking factor to *Phleum pratense*

7.2.2.2. Study Population

Inclusion

Healthy male and female (non-childbearing potential) aged 18 to 65 years with a clinical history of significant allergic rhinoconjunctivitis to grass (with or without asthma) and with a positive skin prick test (average wheal ≥ 5 mm) and positive for specific IgE against *Phleum pratense* (≥ IgE Class 2) and FEV1 ≥ 70% predicted.

Exclusion

Clinical history of symptomatic seasonal allergic rhinitis and/or asthma; receiving immunosuppressive treatment within 3 months prior to screening, clinical history of severe asthma; history of chronic sinusitis during 2 years prior to screening, current severe atopic dermatitis.

7.2.2.3. Study treatments

Subjects were randomised to receive either SCH697243 or placebo in a 1:1 ratio using an interactive voice response system (IVRS). Treatment was for 24 weeks.

Table 33: Study P05238; Rescue medication

RHINOCONJUNCTIVITIS				
STEP	**Rescue Medications**	**Subject Dosing Instruction**	**Requirements for Start of Use**	**Dispensed at Visits**
1	Loratadine 10 mg RediTabs tablet	1 tablet QD	Total symptom score of ≥4 and start of GPS confirmed by site	3A, 4
1b	Olopatadine hydrochloride 0.1% ophthalmic solution	1 drop in each affected eye BID	In addition to loratadine for control of persistent eye symptoms	3A, 4
2	Mometasone furoate monohydrate nasal spray 50 mcg	2 sprays in each nostril QD	Total symptom score of ≥4 despite loratadine. Use in addition to loratadine	3A, 4
3	Prednisone tablet 5 mg (or prednisolone equivalent)	Day 1: 1 mg/kg/day (maximum 50 mg/day); Days 2, 3, 5, and 7: 0.5 mg/kg/day (maximum 25 mg/day)	Total symptom score of ≥4 despite loratadine and mometasone furoate nasal spray. Use in addition to loratadine and mometasone furoate nasal spray.	Unscheduled Visit [a]
ASTHMA				
A	Albuterol sulfate HFA [b] inhalation aerosol 108 mcg/inhalation	2 inhalations every 4 to 6 hours PRN	Asthmatics: Use as needed. New asthmatics: at the investigator's discretion.	Asthmatics: Visits 3A, 4 New asthmatics: Unscheduled Visit [a]
B	Fluticasone propionate HFA [c] inhalation aerosol 44 mcg/inhalation	2 inhalations BID (up to max of 10 inhalations BID)	Four or more albuterol sulfate HFA inhalations/day for 2 days for nocturnal asthma or shortness of breath. Use in addition to albuterol sulfate HFA.	Unscheduled Visit [a]
C	Prednisone tablet 5 mg (or prednisolone equivalent)	Day 1: 1 mg/kg/day (maximum 50 mg/day) Days 2, 3, 5, and 7: 0.5 mg/kg/day (maximum 25 mg/day)	At the investigator's discretion in case of asthma exacerbation. Use in addition to albuterol sulfate HFA and fluticasone propionate HFA inhalations.	Unscheduled Visit [a]

QD = Once daily; BID = Twice daily; PRN = As needed; HFA = hydrofluoroalkane; GPS = Grass pollen season
a: To be dispensed only at Unscheduled Visits taking place after Visits 3A and 4. In countries where prednisone was not available, prednisolone was dispensed in a clinically equivalent dosage.
b: Labelled strength 108 mcg/inhalation (equivalent to 90 mcg albuterol base) in the USA and salbutamol sulphate (100 mcg) in Canada.
c: Labelled strength 44 mcg/inhalation in the USA and 50 mcg/inhalation in Canada.
Source: Study P05238 CSR Table 4 (Section 16.1.1.1)

7.2.2.4. Efficacy outcomes

The primary efficacy endpoint for the study was the combined (sum of) rhinoconjunctivitis daily symptom score (DSS) and rhinoconjunctivitis daily medication score (DMS) averaged over the entire grass pollen season (GPS).

The key secondary endpoints were:

- The average rhinoconjunctivitis DSS for the entire GPS
- The average rhinoconjunctivitis DMS for the entire GPS
- The average weekly rhinoconjunctivitis quality of life total score for the entire GPS

Additional secondary endpoints included:

- The average rhinoconjunctivitis DSS for the peak GPS

- The average rhinoconjunctivitis DMS for the peak GPS
- The percentage of minimal symptom days for the entire GPS
- The change in the WPAI-AS sub-scale scores from randomisation to peak season and to end of season.

7.2.2.5. Statistical methods

For the observational period, the average DSS and DMS for the rhinoconjunctivitis and asthma symptoms for each subject were summarised. For the treatment period, the primary efficacy endpoint of the combined (sum of) rhinoconjunctivitis DSS and DMS averaged over the entire GPS was evaluated using a linear model with asthma status, study site, and treatment group as fixed effects. This model allowed for heterogeneous variance estimates for each treatment group. For the primary endpoint, subjects with at least 1 post baseline diary record with DSS and DMS within the defined pollen season were included. The combined average score was based on all available data during the GPS for each subject. A 2-sided 95% confidence interval of the difference in the adjusted means (adjusted for asthma status, treatment, and study site) between the 2 treatment groups was presented. Also the difference in adjusted means between the 2 treatment groups relative to the adjusted mean of the placebo group was presented as a percentage with corresponding confidence intervals. The secondary endpoints were evaluated using a linear effect model with asthma status, treatment, and study site in the model.

For the following key secondary endpoints, type 1 error rate was to be controlled using the Hochberg's test:

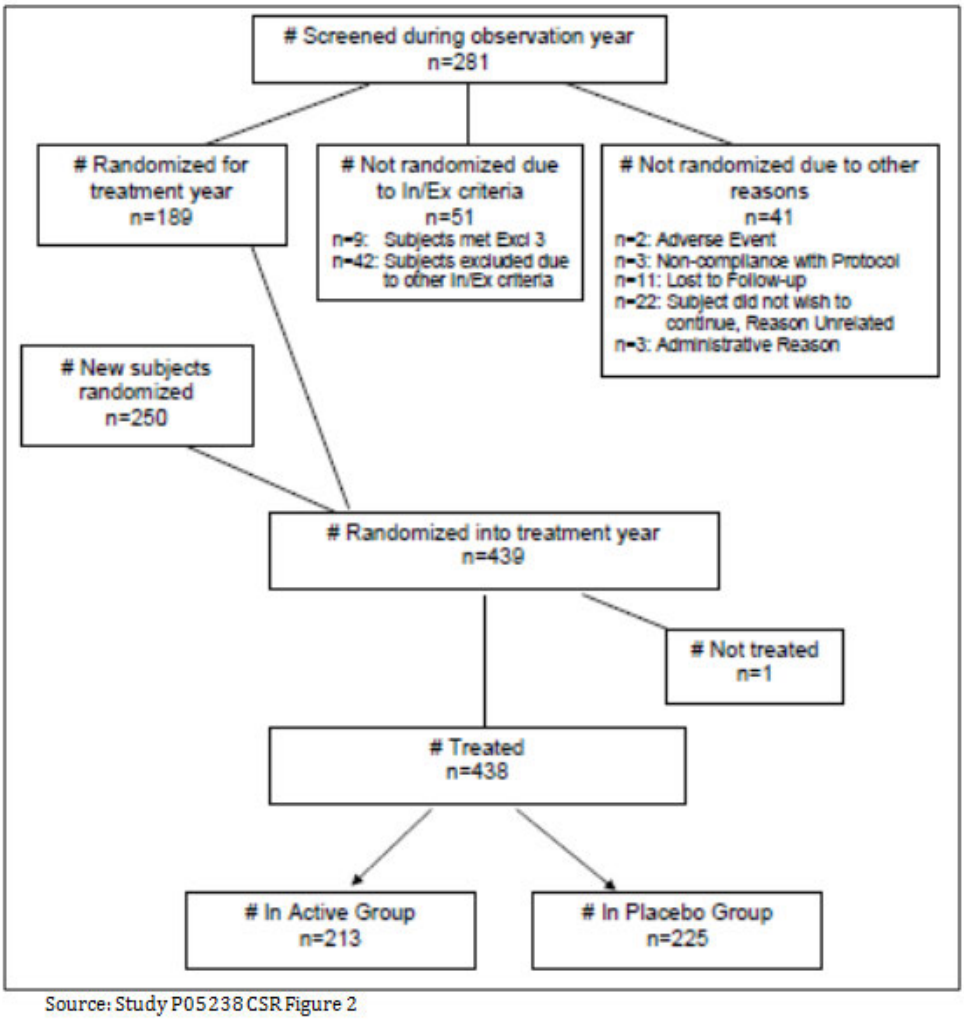
1. SCH 697243 versus placebo on the average rhinoconjunctivitis DSS for the entire GPS
2. SCH 697243 versus placebo on the average rhinoconjunctivitis DMS for the entire GPS
3. SCH 697243 versus placebo on the average weekly rhinoconjunctivitis quality of life total score for the entire GPS

In the observational period, up to 450 subjects were to be enrolled. Assuming a 25% dropout from the observational period, approximately 340 subjects were to be enrolled in the treatment period. New subjects were also to be enrolled after the start of the Year 1 2008 observational period GPS if needed to meet the targeted sample size. With approximately 170 subjects per group, the study was able to detect the following difference from placebo in the primary endpoint with 88% power at a 5% level of significance (2-sided test) (based on results of Study GT-08):

- Difference of effect (%) from placebo to be detected: 1.63 (23%)
- Estimate of mean placebo effect: 7.07
- Estimate of pooled standard deviation (SD): 4.77

7.2.2.6. Participant flow

Figure 12: Study P05238: Study population



Source: Study P05238 CSR Figure 2

Table 34: Study PO5238 Disposition of subjects

Disposition of Subjects	Number (%) of Subjects		
	SCH 697243 (2800 BAU)	Placebo	Total
Treated	213 (100)	225 (100)	438 (100)
Discontinued Treatment Period	38 (18)	33 (15)	71 (16)
Adverse Event	11 (5)	8 (4)	19 (4)
Lost to follow-up	5 (2)	4 (2)	9 (2)
Subject did not wish to continue for reasons unrelated to assigned study treatment	9 (4)	8 (4)	17 (4)
Noncompliance with protocol	12 (6)	12 (5)	24 (5)
Did not meet protocol eligibility	1 (<1)	1 (<1)	2 (<1)
Completed Treatment Period	175 (82)	192 (85)	367 (84)

BAU = Bioequivalent Allergy Unit; 2800 BAU is equal to 75,000 SQ-T
Source: Study P05238 CSR Table 12 (Section 14.4.1)

7.2.2.7. Baseline data

The 2 treatment groups were well-balanced regarding the baseline characteristics. The majority of subjects (91%) were between the ages of 18 and 50 years. An approximately equal percentage of subjects were male and female. The majority of subjects were White (84%), while 10% were Black or African American, 3% were Asian, 3% were multiracial, and 1% were Native Hawaiian or other Pacific Islander. Mean baseline heights and weights were similar between

treatment groups. Body mass index (BMI) was also similar between treatment groups, ranging from 11.6 to 48.4 kg/m^2 (mean of 27. 8 kg/m^2 overall). The median duration of allergic rhinoconjunctivitis at Baseline was 20 years overall (20 years in the SCH 697243 group and 19 years in the placebo group).

Tabulated data was provided.

7.2.2.8. Results for the primary efficacy outcome

The primary outcome was the Total Combined Score (TCS) based upon the combined (sum of) rhinoconjunctivitis daily symptom score (DSS) and daily medication score (DMS) averaged over the entire GPS.

The results of the TCS analysis showed a lower adjusted mean TCS for the SCH 697243 group (5.08) when compared to the placebo group (6.39) [difference = -1.31]. The difference in mean TCS was statistically significant (p = 0.005), and treatment with SCH 697243 provided a 20% improvement over treatment with placebo during the GPS.

Table 35: Study P05238: Summary and analysis of the Total Combined Score (TCS) during the entire GPS (FAS)

	SCH 697243 2800 BAU (n=208)	Placebo (n=225)	Difference (%)	p-value	95% CI
Number of Subjects Included in Analysis	184	207			
Raw Mean(SD)	5.33 (4.5)	6.69 (4.9)			
Adjusted Mean(SE)	5.08 (0.4)	6.39 (0.4)	-1.31(-20%)	0.005	-2.22, -0.40
					(-33%, -6%)
Median	4.62	6.13			
Min, Max	(0.0, 32.6)	(0.0, 25.0)			
95% CI of the Mean	(4.7, 6.0)	(6.0, 7.4)			

SD = Standard Deviation, SE = Standard Error, CI = Confidence Interval, FAS = Full Analysis Set, BAU = Bioequivalent Allergy Unit, ANOVA = Analysis of Variance
Endpoint Score range: TCS: 0-54 (sum of symptom and medication scores) % = Percent reduction in the 2800 BAU group compared to Placebo. Analysis via ANOVA with asthma status, treatment group, and site as fixed effects and adjusting for different error variation for each treatment group.
Source: Study P05238 CSR Table 18 (Section 14.2.1)

Similar results were seen with the PP population.

7.2.2.9. Results for other efficacy outcomes

Rhinoconjunctivitis Daily Score (DSS) during GPS

In the pre-seasonal period, subjects in both groups had low levels of rhinoconjunctivitis symptoms (3.14 in the active group and 3.45 in the placebo group; p = 0.340). As the grass pollen season began, the rhinoconjunctivitis daily symptom score increased in both treatment groups, but to a lesser extent for the group on SCH 697243. Analysis of the rhinoconjunctivitis DSS results during the GPS showed a lower adjusted mean DSS for the SCH 697243 group (3.83) compared to the placebo group (4.69). Treatment with SCH 697243 provided statistically significantly lower rhinoconjunctivitis symptoms (18%; difference = -0.86; p = 0.015, adjusted for multiplicity) compared with placebo.

Table 36: Study P05238: Summary and analysis of the Daily Symptom Score (DSS) during the entire GPS (FAS)

	SCH 697243 2800 BAU (n=208)	Placebo (n=225)	Difference (%)	p-value	Adjusted p-value	95% CI
Number of Subjects Included in Analysis	184	207				
Raw Mean (SD)	3.88 (2.9)	4.79 (3.2)				
Adjusted Mean (SE)	3.83 (0.3)	4.69 (0.3)	-0.86 (-18%)	0.005	0.015	-1.46, -0.26 (-29%, -6%)
Median	3.43	4.52				
Min - Max	(0.0, 16.1)	(0.0, 14.7)				
95% CI of the Mean	(3.5, 4.3)	(4.4, 5.2)				

SD = Standard Deviation, SE = Standard Error, CI = Confidence Interval, BAU = Bioequivalent Allergy Unit, ANOVA = Analysis of Variance, FAS = Full Analysis Set.
Adjusted p-values are based on Benjamini and Hochberg method.
Endpoint Score range: DSS: 0 - 18
% = Percent reduction in the 2800 BAU group compared to Placebo. Analysis via ANOVA with asthma status, treatment group, and site as fixed effects and adjusting for different error variation for each treatment group.
Source: study P05238 CSR Table 19 (Section 14.2.6)

Average Rhinoconjunctivitis DMS during GPS

The use of rescue medication was limited during the treatment period, most probably related to the weak 2009 grass pollen season. The mean DMS for SCH 697243 was not significantly different from that of placebo (difference = -0.45; p = 0.084).

Table 37: Study P05238: Summary and analysis of daily medication score during the GPS (FAS)

	SCH 697243 2800 BAU (n=208)	Placebo (n=225)	Difference (%)	p-value	Adjusted p-value	95% CI
Number of Subjects Included in Analysis	184	207				
Raw Mean (SD)	1.45 (2.5)	1.90 (2.9)				
Adjusted Mean (SE)	1.25 (0.2)	1.70 (0.2)	-0.45 (-26%)	0.084	0.084	-0.96, 0.06 (-49%, -5%)
Median	0.26	0.50				
Min - Max	(0.0, 16.5)	(0.0, 13.9)				
95% CI of the Mean	(1.1, 1.8)	(1.5, 2.3)				

SD = Standard Deviation, SE = Standard Error, CI = Confidence Interval, BAU = Bioequivalent Allergy Unit, ANOVA = Analysis of Variance, FAS = Full Analysis Set
Adjusted p-values are based on Benjamini and Hochberg method.
Endpoint Score range: DMS: 0 - 36
% = Percent reduction in the 2800 BAU group compared to Placebo. Analysis via ANOVA with asthma status, treatment group, and site as fixed effects and adjusting for different error variation for each treatment group.
Data Source: Study P05238 CSR Table 20 (Section 14.2.7)

Average weekly rhinoconjunctivitis quality of life total score during GPS

The analysis of the average weekly RQLQ(S) total score during the GPS (evaluated on the FAS) showed a statistically significantly lower total score for subjects treated with SCH 697243 compared to placebo (mean total scores of 1.30 and 1.57, respectively; p = 0.022, adjusted for multiplicity). Subjects treated with SCH 697243 demonstrated a 17% lower total score compared to placebo.

Table 38: Study P05238: Summary and analysis of RQLQ(S) Total Score during GPS (FAS)

	SCH 697243 2800 BAU (n=208)	Placebo (n=225)	Difference (%)	p-value	Adjusted p-value	95% CI
Number of Subjects Included in Analysis	172	197				
Raw Mean (SD)	1.27 (1.1)	1.56 (1.1)				
Adjusted Mean (SE)	1.30 (0.1)	1.57 (0.1)	-0.27 (-17%)	0.015	0.022	-0.48, -0.05 (-29%, -4%)
Median	1.01	1.45				
Min - Max	(0.0, 5.1)	(0.0, 5.8)				
95% CI of the Mean	(1.1, 1.4)	(1.4, 1.7)				

SD = Standard Deviation, SE = Standard Error, CI = Confidence Interval, BAU = Bioequivalent Allergy Unit, FAS = Ful Analysis Set, ANOVA = Analysis of Variance.
Adjusted p-values are based on Benjamini and Hochberg method.
Endpoint Score range: RQLQ(S) Total Score: 0 - 6 (mean of all domain scores).
RQLQ(S) total score during GPS is calculated as the average of weekly assessments during this period.
% = Percent reduction in the 2800 BAU group compared to Placebo. Analysis via ANOVA with asthma status, treatment group, and site as fixed effects and adjusting for different error variation for each treatment group.
Source: Study P05238 CSR Table 21 (Section 14.2.8)

The change from baseline to the average total score during the GPS in RQLQ(S) was found to be statistically significantly different between treatment groups (p = 0.020); treatment with SCH 697243 provided 34% less impairment from baseline in quality of life domain symptoms compared to the placebo group (0.41 versus 0.62, respectively)

Results for the additional efficacy outcomes of total combined score (TCS) and average rhinoconjunctivitis DSS and DMS for the peak GPS were provided.

Immunological assessments

Details of the immunological assays used were provided.

Phleum Pratense specific IgE

Higher $\log_{10}$-transformed IgE values were seen in the SCH 697243 group than in the placebo group at both peak season and end-of-season ($p < 0.001$ for each).

The SCH 697243 group exhibited a larger change from baseline to both peak season and end-of-season with notably higher $\log_{10}$-transformed IgE values ($p < 0.001$) compared to the placebo group.

Table 39: Study P05238: Summary and analysis of log_{10}(IgE) (kU/L) immunological assessment by visit (FAS)

Study Period	SCH 697243 2800 BAU n=208	Placebo n=225	Difference	p-value	95% CI
Baseline					
n	201	218			
Raw Mean (SD)	0.90 (0.69)	0.90 (0.70)			
Median	0.95	0.99			
Min - Max	(-1.54, 2.42)	(-1.14, 2.47)			
Peak Season					
n	178	195			
Raw Mean (SD)	1.41 (0.80)	0.89 (0.75)			
Adjusted Mean (SE)	1.32 (0.07)	0.77 (0.06)	0.55	<0.001	(0.40, 0.70)
Median	1.56	0.97			
Min - Max	(-1.55, 2.79)	(-1.36, 2.47)			
95% CI of the Mean	(1.29, 1.53)	(0.78, 0.99)			
End-of-Season					
n	199	211			
Raw Mean (SD)	1.43 (0.74)	1.02 (0.73)			
Adjusted Mean (SE)	1.36 (0.06)	0.93 (0.06)	0.43	<0.001	(0.30, 0.56)
Median	1.52	1.11			
Min - Max	(-1.55, 2.76)	(-1.45, 2.62)			
95% CI of the Mean	(1.32, 1.53)	(0.92, 1.12)			

SD = Standard Deviation, SE = Standard Error, CI = Confidence Interval, BAU = Bioequivalent Allergy Unit, FAS = Full Analysis Set, ANOVA = Analysis of Variance.
Adjusted Means via ANOVA model with asthma status, treatment group, and site as fixed effects.
Source: Study P05238 CSR Table 28 (Section 14.2.18.2.1)

Phleum pratense specific IgG4

Notably higher log_{10}-transformed IgG4 values were seen in the SCH 697243 group than in the placebo group at both peak season and end-of-season ($p < 0.001$ for each). Induction of IgG4 antibodies may have an inhibitory role with respect to the IgE mediated response that results in allergic symptomology. For the SCH 697243 group, a marked increase in IgG4 level was observed over time from baseline to peak season, with IgG4 levelling off from peak season through the end-of-season. The increase in IgG4 antibodies is induced by treatment with grass AIT. For the placebo group, no change in IgG4 levels was observed. The SCH 697243 group exhibited a larger change in log_{10}-transformed IgG4 values from baseline ($p < 0.001$) than the placebo group, indicating that grass AIT has a specific effect on the immune response.

Table 40: Study P05238: Summary and analysis of log_{10}(IgG4) (mg/L) immunological assessment by visit (FAS)

Study Period	SCH 697243 2800 BAU n=208	Placebo n=225	Difference	p-value	95% CI
Baseline					
n	198	220			
Raw Mean (SD)	-0.68 (0.54)	-0.71 (0.55)			
Median	-0.73	-0.69			
Min - Max	(-2.52, 0.67)	(-2.08, 0.71)			
Peak Season					
n	178	194			
Raw Mean (SD)	-0.25 (0.62)	-0.71 (0.56)			
Adjusted Mean (SE)	-0.29 (0.05)	-0.75 (0.05)	0.46	<0.001	(0.35, 0.58)
Median	-0.22	-0.69			
Min - Max	(-1.72, 1.28)	(-2.15, 0.68)			
95% CI of the Mean	(-0.34, -0.16)	(-0.79, -0.63)			
End-of-Season					
n	195	210			
Raw Mean (SD)	-0.24 (0.63)	-0.67 (0.55)			
Adjusted Mean (SE)	-0.29 (0.05)	-0.72 (0.05)	0.43	<0.001	(0.30, 0.54)
Median	-0.20	-0.68			
Min - Max	(-2.32, 1.25)	(-2.04, 0.73)			
95% CI of the Mean	(-0.33, -0.15)	(-0.75, -0.60)			

SD = Standard Deviation, SE = Standard Error, CI = Confidence Interval, BAU = Bioequivalent Allergy Unit,
FAS = Full Analysis Set, ANOVA = Analysis of Variance.
Adjusted Means via ANOVA model with asthma status, treatment group, and site as fixed effects.
Source: Study P05238 CSR Table 30 (Section 14.2.18.2.2)

Phleum pratense specific IgE-blocking factor

For the placebo group, no difference in the proportion of IgE prevented from binding to allergen was observed over time (that is, no change in the level of IgE-blocking antibodies over time). For the SCH 697243 group, a marked increase in IgE-blocking factor values was observed from baseline to peak season, with these values levelling off from peak season to end-of-season. For the placebo group, no difference in the proportion of IgE prevented from binding to allergen was observed over time (that is, no change in the level of IgE-blocking antibodies over time). For the SCH 697243 group, a marked increase in IgE-blocking factor values was observed from baseline to peak season, with these values levelling off from peak season to end-of-season. The SCH 697243 group exhibited a notably larger change in IgE-blocking factor values from baseline ($p < 0.001$) than the placebo group, indicating that treatment with SCH 697243 effectively blocks *Phleum pratense* specific IgE from binding to allergen.

Table 41: Study P05238: Summary and analysis of IgE blocking factor (1-lgX) by visit (FAS)

Study Period	SCH 697243 2800 BAU n=208	Placebo n=225	Difference	p-value	95% CI
Baseline					
n	194	212			
Raw Mean (SD)	-0.03 (0.17)	-0.06 (0.19)			
Median	-0.02	-0.04			
Min - Max	(-0.56, 0.62)	(-0.51, 0.53)			
Peak Season					
n	172	185			
Raw Mean (SD)	0.10 (0.25)	-0.05 (0.18)			
Adjusted Mean (SE)	0.09 (0.02)	-0.06 (0.02)	0.15	<.001	(0.11, 0.20)
Median	0.10	-0.04			
Min - Max	(-0.75, 0.81)	(-0.61, 0.37)			
95% CI of the Mean	(-0.07, -0.14)	(-0.08, -0.03)			
End-of-Season					
n	193	206			
Raw Mean (SD)	0.11 (0.24)	-0.05 (0.19)			
Adjusted Mean (SE)	0.11 (0.02)	-0.05 (0.02)	0.15	<.001	(0.11, 0.20)
Median	0.10	-0.04			
Min - Max	(-0.70, 0.81)	(-0.58, 0.40)			
95% CI of the Mean	(0.07, 0.14)	(-0.08, -0.03)			

SD = Standard Deviation, SE = Standard Error, CI = Confidence Interval, BAU = Bioequivalent Allergy Unit,
FAS = Full Analysis Set, ANOVA = Analysis of Variance.
Adjusted Means via ANOVA model with asthma status, treatment group, and site as fixed effects.
Subset of subjects with baseline and at least 1 post baseline assessment
Source: Study P05238 CSR Table 32 (Section 14.2.18.2.3)

7.2.3. Other studies

Study GT-10 and GT-17 which evaluated treatment compliance were summarised.

7.3. Indication 2: Treatment of allergic rhinitis with or without conjunctivitis in children (≥ 5 years)

7.3.1. Pivotal efficacy study; Study GT-12

A Phase III Trial investigating the efficacy and safety of Grazax in children aged 5 to 16 years with grass pollen induced rhinoconjunctivitis with or without asthma.

7.3.1.1. Study design, objectives, locations and dates

A randomised, parallel group, double blind, placebo controlled study conducted at 26 sites in Germany from November 2006 to September 2007.

Primary objective

To evaluate the efficacy of Grazax 75,000 SQ-T compared to placebo in children aged 5 to 16 years with grass pollen induced rhinoconjunctivitis (with and without asthma), based on the rhinoconjunctivitis symptom and medication scores during the entire grass pollen season.

Secondary objectives

To evaluate the efficacy and safety of Grazax 75,000 SQ-T compared to placebo in children aged 5 to 16 years with grass pollen induced rhinoconjunctivitis (with and without asthma), based on secondary endpoints including asthma endpoints.

7.3.1.2. Inclusion and exclusion criteria

Inclusion

Healthy boys and girls (non-childbearing potential) aged 5 to 16 years with clinical history of grass pollen induced allergic rhinoconjunctivitis (with or without asthma) having received

treatment, during the previous grass pollen season; with positive SPT response (wheal diameter > 3 mm) to *Phleum pratense* and positive specific IgE against *Phleum pratense* (≥ IgE class 2).

Exclusion

A clinical history of symptomatic seasonal allergic rhinitis and/or asthma; having received regular medication due to another allergen during or potentially overlapping the grass pollen season; perennial allergic rhinitis and/or asthma; history or chronic sinusitis during the past 2 years; clinical history of severe asthma (GINA Step 4 and children who are treated with inhaled corticosteroids and additionally short-acting β2-agonists and whose FEV1 is still < 80% of the expected value).

7.3.1.3. Study treatments

Subjects were randomised to receive either Grazax 75,000 SQ-T or placebo once daily. The tablet was to be administered at the time of day which allowed the parent/guardian to keep the subject under observation for adverse events. The tablet was placed under the tongue and kept there for 1 minute before swallowing. Eating and drinking was not allowed for 5 minutes after administration. Treatment was for 16 weeks prior to and then during the entire GPS of 2007 that is total of 26 weeks.

Rescue medication

Rescue medication was provided to subjects in addition to the IMP as pre-defined, open label medication in a step wise fashion depending on the severity, persistency and type of symptoms. In all cases the investigator was to be contacted for evaluation of the rhinoconjunctivitis symptoms prior to the use of rescue medication. Rescue medication for rhinoconjunctivitis symptoms was provided in the following steps as shown in Table 42 and for asthma medication as shown in Table 43.

Table 42: Study GT-12; steps for rescue medication use for rhinoconjunctivitis symptoms

Step 1	Lorano (loratadine tablets):10 mg	
Dosing	5-12 years, < 30 kg:	½ tablet (5 mg) daily
	5-12 years, > 30 kg	1 tablet (10 mg) daily
	13-16 years	1 tablet (10 mg) daily
Step 1b	Livocab direkt (levocabastine eye drops): 0.5 mg/ml	
Dosing	5-16 years	1 drop in affected eye(s) twice daily max. 2×1 drop per eye per day
Step 2	Aquacort (budesonide nasal spray): 50 µg	
Dosing	-12 years	Day1: 1×100 µg per nostril
		Day 2 + 1×50 µg per nostril per day
	13-16 years	Day1: 1×200 µg per nostril
		Day 2 + 1×100 µg per nostril per day
Step 3	Prednisolon AL (prednisolone tablets): 5 mg	
Dosing		Day 1: 1 mg per kg bodyweight per day, max. 50 mg per day
		Day 2, 3, 5 and 7: 0.5 mg per kg bodyweight per day, max. 25 mg per day

Table 43: Study GT-12 steps for rescue medication for asthma symptoms

Step A Dosing	Salbutamol (salbutamol inhaler or spray): 0.10%	
	5-12 years	1 inhalation twice daily max. 4 inhalations per day
	13-16 years	2 inhalations twice daily max. 4 × 2 inhalations per day
Step B Dosing	Flutide (fluticasone inhaler or spray): 125 or 250 µg	
	5-12 years	125 µg, 1-2 inhalations daily
	13-16 years	250 µg, 1-2 inhalations daily
Step C Dosing	Prednisolon AL (prednisolone tablets): 5 mg	
		Day 1: 1 mg per kg bodyweight per day, max. 50 mg per day
		Day 2, 3, 5 and 7: 0.5 mg per kg bodyweight per day, max. 25 mg per day

Table 44: Study GT-12 Rescue medication dose scores

Step	Rhinoconjunctivitis rescue medication	Score/dose [1]	Max daily score
1	Loratadine tablets, 5 or 10 mg	6	6
1b	Levocabastine eye drops, 0.5 mg/ml	1	4
2	Budesonide nasal spray, (5-12 years, Day 1) 100 µg/dose	4	8
2	Budesonide nasal spray, (5-12 years, Day 2+) 50 µg/dose	4	8
2	Budesonide nasal spray, (13-16 years, Day 1) 200 µg/dose	4	8
2	Budesonide nasal spray, (13-16 years, Day 2+) 100 µg/dose	4	8
3	Prednisolone tablets 5 mg, Day 1 [2]	1.6	16
3	Prednisolone tablets 5 mg, Day 2+ [2]	3.2	16
	Maximum daily rhinoconjunctivitis medication score		**34**
	Asthma rescue medication	**Score/dose [1]**	**Max daily score**
A	Salbutamol spray (5-12 years) 100 µg/dose	2	8
A	Salbutamol spray (13-16 years) 100 µg/dose	1	8
B	Fluticasone inhaler/spray, 125 µg or 250 µg	4	8
C	Prednisolone tablets 5 mg, Day 1 [2]	1.6	16
C	Prednisolone tablets 5 mg, Day 2+ [2]	3.2	16
	Maximum daily asthma medication score		**32**

1 Scoring scales were not seen by the subjects
2 Use of prednisolone counts in the rhinoconjunctivitis score and/or in the asthma score depending on the reason stated in the diary record.
For budesonide and prednisolone day1 and day2+ are defined as follows:
Budesonide:
Day 1: No budesonide must have been taken the previous day.
Day 2+: Budesonide must have been taken the previous day.
If there is no record on the previous day, the record two days ago is used instead to define the day as either day1 or day2+.
If there is no record on the two previous days, the day is defined as day1.
Prednisolone:
Day 1: No prednisolone must have been taken on the two previous days.
Day 2+: Prednisolone must have been taken on at least one of the two previous days.
A missing record is set equal to no intake of prednisolone.

7.3.1.4. Efficacy variables and outcomes

The primary efficacy outcomes were the average daily rhinoconjunctivitis symptom and medication scores. These two average scores were calculated as the sum of the individual daily scores for each subject during the entire grass pollen season 2007 divided by the number of subject diary recordings of that score during the entire grass pollen season.

The secondary efficacy outcomes included:

- The average rhinoconjunctivitis symptom score in the peak GPS
- The average rhinoconjunctivitis medication score in the peak GPS
- The percentage of rhinoconjunctivitis "well days" in the entire GPS
- The average asthma symptom score in the entire and in the peak GPS

- The average asthma medication score in the entire and in the peak GPS
- Two combined rhinoconjunctivitis symptom and medication scores calculated for each subject for the entire and peak GPS, (a total of four scores)
- The percentage of rhinoconjunctivitis "well days" in the peak GPS
- "Excellent rhinoconjunctivitis control", defined as more than 50% "well days" in the entire GPS
- The average daily rhinoconjunctivitis symptom score assessed on a visual analogue scale (VAS), during the entire and peak GPS.
- Global Evaluation of treatment efficacy (overall comparison of the GPS 2007 compared to previous seasons).
- Immunological parameters (IgE, IgG4 and IgE-blocking antibodies), assessed from serum samples drawn at screening, the pre-season visit, the on-season visit and after the end of the trial.

7.3.1.5. Randomisation and blinding methods

The randomisation was done by the sponsor but details of the method of randomisation are not provided in the CSR.

The trial was double blind with the placebo tablets being similar to the Grazax tablets as regards appearance, smell and taste.

7.3.1.6. Analysis populations

Full-analysis set (FAS): all randomised subjects.

Per-protocol set (PP): all subjects in the FAS who did not violate the inclusion/exclusion criteria significantly; did not take prohibited medication in the period just prior to onset of grass pollen season; had sufficient trial drug compliance, defined as at least 75% of drug compliance (number of tablets used compared to number of treatment days); provided sufficient diary data, defined as at least 50% of diary data in the entire grass pollen season; had received sufficient pre-seasonal treatment, defined as the date of first IMP-intake occurring 8 weeks or more before the start of the grass pollen season in the area of residence of the subject in question and did not have any other significant protocol deviations influencing the primary efficacy endpoint.

7.3.1.7. Sample size

The power calculation was based on the first of the two primary endpoints, the rhinoconjunctivitis symptom score. A total of 300 subjects were planned for randomisation. Assuming a withdrawal rate of 20% and a 1:1 ratio of randomisation, a sample size of 150 per treatment group yields 90% probability for detecting a treatment effect of 21.2% of Grazax 75,000 SQ-T compared to placebo, with a significance level of 5%. In the first year of treatment in Study GT-08 in adults, the treatment effect was 31% and 39% with regards to the symptom and medication scores respectively ($p < 0.0001$ for both).

7.3.1.8. Statistical methods

All statistical tests were assessed using a nominal two-sided significance level of 5%. The null hypothesis was the hypothesis of no difference, and the alternative to the null hypothesis was the hypothesis of difference. Two comparisons were evaluated and the approach to this issue of multiple comparisons was a hierarchical ordering of the null hypotheses. Hence, no statistical conclusions were based on the test of a null hypothesis with a rank lower than or equal to the null hypothesis that was the first not to be rejected. As the ranking of the null hypotheses was pre-specified, formal adjustment for multiple testing was unnecessary.

The ranking of the null hypotheses was as follows:

1. Grazax equals placebo on rhinoconjunctivitis symptom score
2. Grazax equals placebo on rhinoconjunctivitis medication score

Neither the rhinoconjunctivitis symptom nor the medication score data fulfilled the assumption of a normal distribution, as revealed by plotting residuals in normal quantile plots.

For the rhinoconjunctivitis symptom score, the comparison of the 2 treatment groups was performed using an ANOVA with the square-root of the average rhinoconjunctivitis symptom score as response variable, treatment group as a fixed effect and pollen region as random effects. Different residual variances were specified for each treatment group in the ANOVA. The resulting adjusted means for the 2 treatment groups with 95% CI for the square root transformed data were back-transformed to the original scale by squaring. The outcome of this parametric analysis was represented as the difference in the back-transformed, adjusted means between the 2 groups, with a 2-sided 95% CI as well as the coherent p-value. In addition, the difference in back-transformed, adjusted means between the 2 treatment groups relative to the back-transformed, adjusted mean of the placebo group was presented as a percentage with 2-sided 95% CI. The CI for the relative difference was calculated using Fieller's theorem. Finally, a p-value describing the statistical significance of the pollen region is also presented.

For the rhinoconjunctivitis medication score, transformation of the data did not result in an adequate approximation to a normal distribution. Therefore, the comparison of the two treatment groups was performed using the non-parametric Wilcoxon rank sum test. The exact p-value of the Wilcoxon rank sum test was calculated using Monte Carlo estimation. The Hodges-Lehmann estimator of a difference associated with the Wilcoxon rank sum test was also calculated, together with a 95% CI. The Hodges-Lehmann difference was also expressed as a relative difference in percent by dividing with the median of the placebo group and multiplying with 100%. Finally, the individual medians for the two treatment groups are reported, with 95% CI. In addition, the absolute and relative (percent) differences of the medians were reported.

No imputation of data was carried out for the described efficacy analyses, except for the excellent rhinoconjunctivitis control endpoint where withdrawals due to adverse events were counted as not having excellent control.

For the primary endpoints "Average daily rhinoconjunctivitis symptom score, entire season" and "Average daily rhinoconjunctivitis medication score, entire season", a sensitivity analysis was performed, using the Last Observation Carried Forward (LOCF) method for imputation of missing daily diary records. In the LOCF-imputed data set all missing diary records between the first and last diary date was replaced for each subject by the previous non-missing record. This method was only applicable to subjects with at least 1 diary record.

7.3.1.9. Participant flow

Table 45: Study GT-12: Summary of subject disposition

Treatment Group	Grazax		Placebo		Total	
	N	%	N	%	N	%
Screened					307	
Full Analysis Set (FAS)	126	100	127	100	253	100
Per Protocol Set (PP)	91	72	100	79	191	75
Subjects withdrawn	12	10	7	6	19	8
Reason for withdrawal						
Adverse event	4	3	2	2	6	2
Lost to follow-up	2	2	0	0	2	<1
Subject non-compliance	3	2	2	2	5	2
Withdrawal of consent	0	0	1	<1	1	<1
Other	3	2	2	2	5	2
Withdrawal initiated by						
Investigator	5	4	1	<1	6	2
Sponsor	3	2	1	<1	4	2
Subject	4	3	5	4	9	4

N: Number of subjects.
Source: Study GT-12 CSR Panel 7-1 (Table 1.1)

7.3.1.10. Major protocol violations/deviations

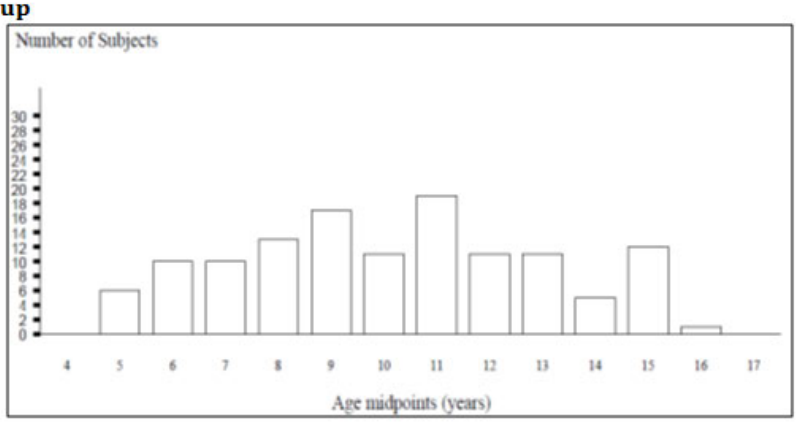
A total of 29 subjects from 17 different centres took prohibited concomitant medications during the trial and were excluded from the PP set as a consequence. Five subjects did not meet the inclusion/exclusion criteria and 1 subject withdrew prior to grass pollen season. A number of other minor procedural violations are noted but do not appear to impact on the analysis.

7.3.1.11. Baseline data

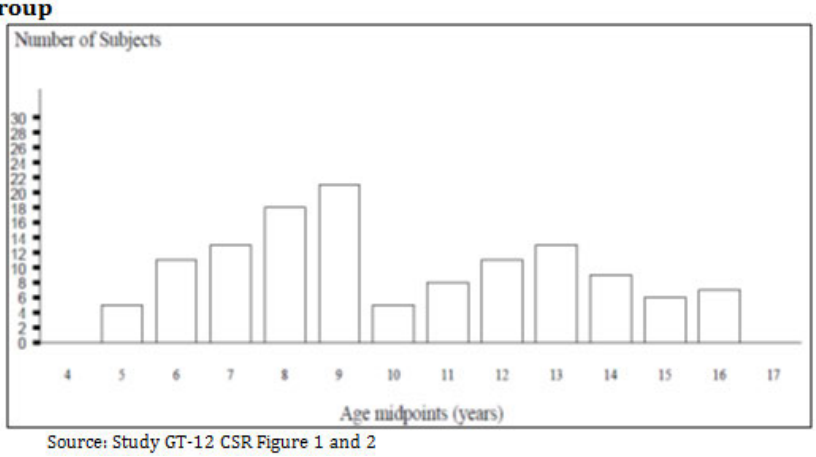
The trial population comprised close to twice as many male subjects (66%) as female (34%) subjects evenly distributed between the two treatment groups. Only a few subjects (3%) were non-Caucasian, and only a few (2%) were smokers. The latter were all found in the placebo group. Mean and median age was similar between the two groups and the proportion of subjects with severe grass pollen allergy was slightly lower for the placebo group (24% versus 31% for the Grazax group). The proportion of subjects with a history of asthma was similar between the two treatment groups. No major differences in skin prick test results were observed between the two treatment groups.

Figure 13: Study GT-12: Age distribution

Grazax Group



Placebo group



Source: Study GT-12 CSR Figure 1 and 2

For baseline body measures and vital signs, there were no major differences observed between the 2 treatment groups.

Tabulated baseline data was provided.

7.3.1.12. Results for the primary efficacy outcome

Average daily rhinoconjunctivitis symptom (DSS) score

The parametric analysis of the average rhinoconjunctivitis symptom score showed a statistically significant difference in favour of the Grazax group compared with the placebo group ($p = 0.0215$). The difference relative to placebo between the back-transformed, adjusted means for the two treatment groups was 22%. In addition, a non-parametric analysis for the FAS of the symptom score over the entire grass pollen season confirmed the observed treatment effect, with a difference relative to placebo between the medians of the two treatment groups of 24%.

Table 46: Study GT-12: Analysis of average rhinoconjunctivitis symptom score, entire grass pollen season (FAS)

	N	Estimate	95% CL	p-value
Parametric analysis				
Grazax, adjusted mean	117	2.18	[1.82; 2.58]	
Placebo, adjusted mean	121	2.80	[2.45; 3.18]	
Difference (Placebo–Grazax)		0.62	[0.10; 1.15]	0.0215
Difference relative to placebo (%)		22.24	[3.74;37.59]	
Non-parametric analysis				
Grazax, median	117	2.13	[1.83; 2.69]	
Placebo, median	121	2.80	[2.27, 3.39]	
Difference (Grazax–placebo)		0.67		
Difference relative to placebo (%)		23.78		
Hodges-Lehmann estimate (Placebo–Grazax)		0.56	[0.09; 1.03]	0.0195

N: Number of subjects with diary data. CL: Confidence limits.
Parametric analysis: ANOVA, square-root-transformed data, adjusted means with 95% confidence intervals back transformed by squaring.
Non-parametric analysis: Wilcoxon rank sum test with the associated Hodges-Lehmann estimate for a difference.
Source: Study GT-12 Panel 9-3 (Tables 3.7.1 and 3.7.2)

The results were similar for the PP analysis.

Rhinoconjunctivitis rescue medication score (DMS)

Subjects treated with Grazax had an overall lower medication intake than subjects treated with placebo, mainly due to a reduction in the use of loratadine tablets.

Table47: Study GT-12; Analysis of average rhinoconjunctivitis medication score, entire grass pollen season (FAS)

	N	Estimate	95% CL	p-value
Non-parametric analysis				
Grazax, median	117	0.78	[0.43; 1.30]	
Placebo, median	121	1.19	[0.74, 2.64]	
Difference (Grazax–placebo)		0.41		
Difference relative to placebo (%)		34.25		
Hodges-Lehmann estimate (Placebo–Grazax)		0.31	[0.01; 0.68]	0.0156

N: Number of subjects with diary data. CL: Confidence limits.
Non-parametric analysis: Wilcoxon rank sum test with the associated Hodges-Lehmann estimate for a difference.
Source: Study GT-12 CSR Panel 9-5 (Table 3.8.1)

The results were similar for the PP analysis.

An amendment to the CSR was submitted in which the results of the medication score were further analysed. This was due to the finding of a configuration deficiency in the programming of the electronic log pads used for assessment of symptoms and medication use. This deficiency resulted in 42 diary records with inconsistent responses to 2 questions regarding the use of rescue medication. The amendment provided a sensitivity analysis for the impact of this deficiency on the statistical analysis of the rhinoconjunctivitis medication score. The clinical database contained an inconsistency in the records regarding the use of budesonide (Aquacort). For these records, a value > 0 is present for the number of puffs of Aquacort taken that day although the same diary record contains a "No" as the answer to the question "Did your child take any Aquacort nasal spray today?" In the original CSR, the number of puffs entered was used in the analysis of the medication score, as the protocol specified that all data should be used to its full extent with no imputation or alteration of data. However, it may be argued that the 42 inconsistent diary records may represent no use of Aquacort on the concerned day.

The result of the sensitivity analysis was that the medians for the medication score was slightly lower for both treatment groups in the sensitivity analysis compared to the original analysis. This led to a slightly lower absolute difference between the 2 treatment groups, giving a relative

difference of 33% in the sensitivity analysis instead of 34%. For both the original analysis and the sensitivity analysis, the difference between the 2 treatment groups is highly statistically significant (p = 0.0156 compared with p = 0.0175), indicating only very small difference for the 2 analytical approaches.

7.3.1.13. Results for other efficacy outcomes

Table 48: Study GT-12; Other efficacy outcomes

Endpoint (FAS)	75,000 SQ-T (mean)	Placebo (mean)	p-value	Reduction (%)
Average rhinoconjunctivitis symptom score – peak GPS parametric	2.84	3.91	0.0059	27
Average rhinoconjunctivitis symptom score – peak GPS Non-parametric	2.93	3.93	0.0139	25
Rhinoconjuctivitis medication score – peak GPS	0.87*	2.40*	0.0013	64
Percentage of well days – entire GPS - parametric	51.57	42.33	0.0225	22
Percentage of well days – entire GPS – non-parametric	53.23	41.57	0.0235	28
Asthma symptom score – non-parametric	0.06*	0.16*	0.0344	64
Asthma medication score -	0.00*	0.00*	0.2023	0
Percentage of day with asthma symptoms - parametric	5.10	10.56	0.027	
Percentage of day with asthma symptoms – non-parametric	4.55	12.16	0.033	63
Rhinoconjunctivitis combined score 1 - parametric	3.70	4.87	0.0216	24
Rhinoconjunctivitis combined score 1 – non-parametric	3.43	4.95	0.0132	31
Rhinoconjunctivitis combined score 2 – non-parametric	0.13	0.18	0.0083	27
Average number of well days	40.61	28.20	0.0042	12
Excellent rhinoconjunctivitis control	55.56	39.67	0.019	16
VAS score – entire GPS	13.82	11.03	0.1018	20
VAS score – peak GPS	18.56	14.05	0.0534	24
Global evaluation	7395	65.57	0.164	13

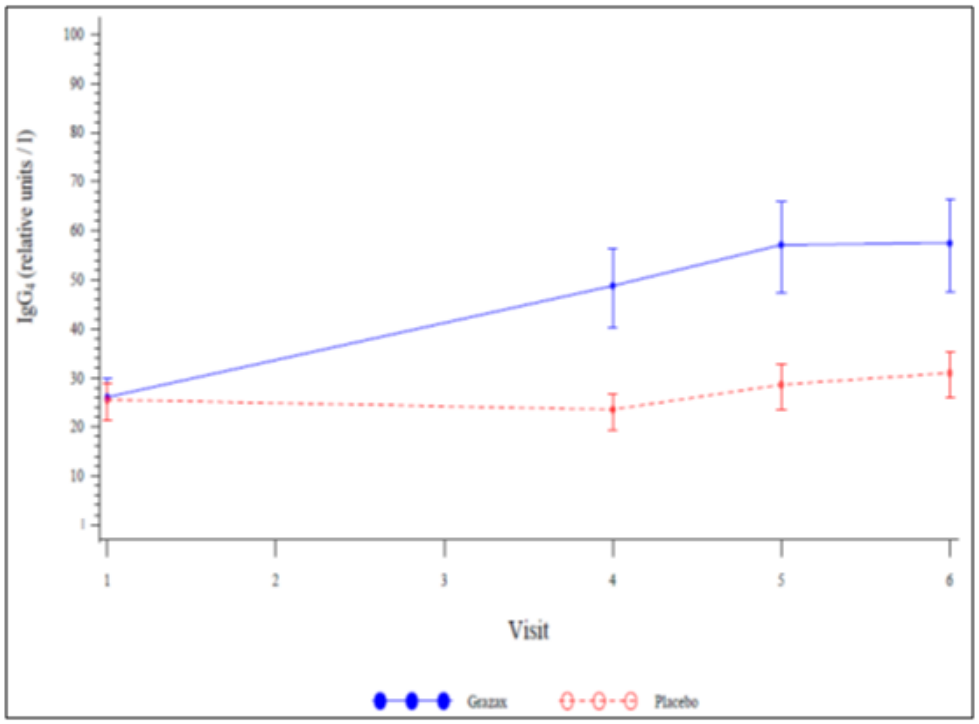
Parametric analysis: ANOVA, square-root-transformed data, adjusted means with 95% confidence intervals back transformed by squaring.
Non-parametric analysis: Wilcoxon rank sum test with the associated Hodges-Lehmann estimate for a difference.
* median values
"Combined score 1": S + M "Combined score 2": $\frac{S/S_{max}}{1-(M_{max}-0.1)/M_{max}}$
S = daily symptom score; S_{max} = maximum possible daily symptom score
M = daily medication score; M_{max} = maximum possible daily medication score.
Source: Study GT-12 CSR adapted from Panels 9-6, 9-7, 9-9, 9-10, 9-15, 9-16, 9-21, 9-22, 9-23 and Tables 3.11.1, 3-13.1 and 3.1

Immunological markers

IgG4

For the placebo group, a very small decrease in IgG4 was seen from screening to the pre-season visit, followed by a slight increase during the grass pollen season. For the Grazax group, a constant increase was observed prior to the season, numerically larger than that observed for the placebo group. For each visit, the treatment effect is statistically significantly larger for the subjects treated with Grazax than those treated with placebo.

Figure 14: Study GT-12; Mean IgG4 antibody levels at different time points (FAS)



Source: Study GT-12 CSR Panel 9-24 (Figure 12 and Table 2.12)

Table 49: Study GT-12; IgG4 antibodies; parametric analysis of the difference (Grazax–placebo) in treatment effect for each visit compared to the screening visit (Visit 1)

	Estimate	SD	95% CL	p-value
Pre-season (visit 4)	24.01	3.36	[17.37;30.65]	<0.001
On-season (visit 5)	28.60	4.09	[20.50;36.69;]	<0.001
End-of-season (visit 6)	27.05	4.14	[18.86; 35.24]	<0.001

SD: Standard deviation. CL: Confidence limits.
Parametric analysis: ANOVA, untransformed data.
Source: Study GT-12 CSR Panel 9-25 (Table 3.6)

IgE-blocking antibodies

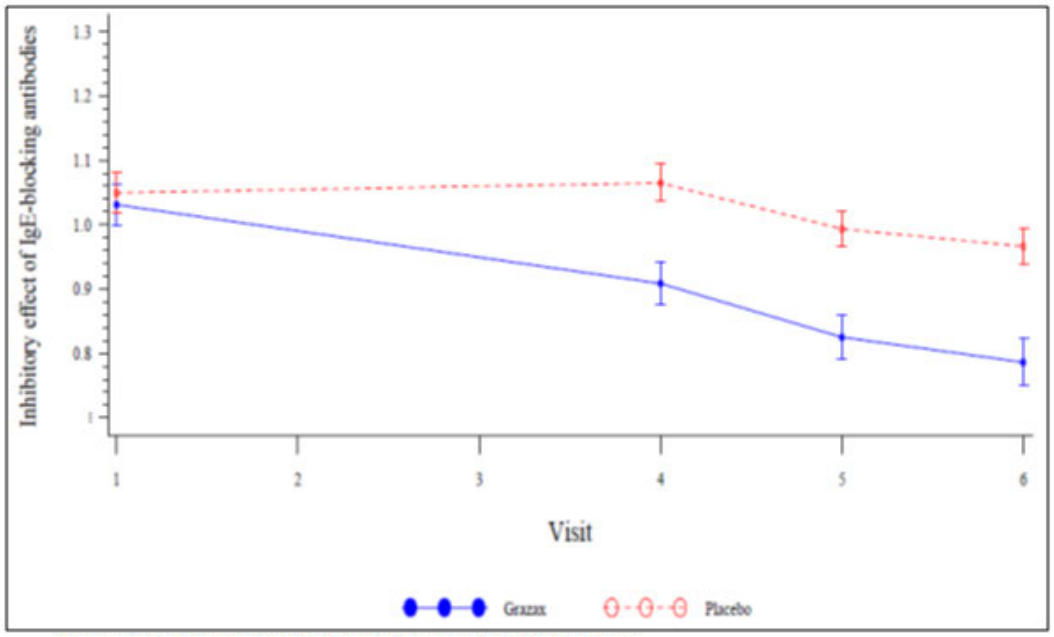
For the placebo group, no difference was observed from screening to the pre-season visit, followed by a slight decrease during the grass pollen season in the fraction of IgE allowed to bind to allergen. For the Grazax group, a constant decrease was observed, numerically larger than that observed for the placebo group. For each visit, the treatment effect is statistically significantly larger for the subjects treated with Grazax than those treated with placebo.

Table 50: Study GT-12; IgE-blocking antibodies; parametric analysis of the difference (placebo versus Grazax) in treatment effect for each visit compared to the screening visit (Visit 1)

	Estimate	SD	95% CL	p-value
Pre-season (visit 4)	0.15	0.02	[0.12;0.18]	<0.001
On-season (visit 5)	0.15	0.02	[0.12;0.19]	<0.001
End-of-season (visit 6)	0.17	0.02	[0.13; 0.21]	<0.001

SD: Standard deviation. CL: Confidence limits.
Parametric analysis: ANOVA, untransformed data.
Source: Study GT-12 CSR Panel 9-27 (Table 3.6)

Figure 15: Study GT-12; Mean of the effect of IgE-blocking antibodies (evaluated by the IgX assay) at different time points (FAS)

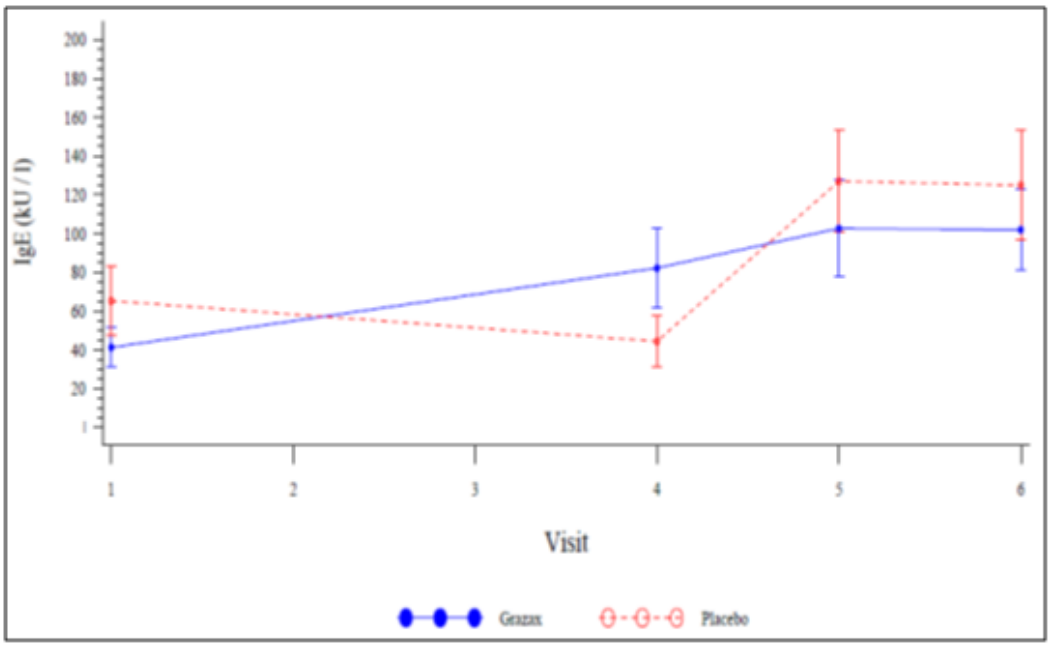


Source: Study GT-12 CSR Panel 9-24 (Figure 13 and Table 2.12)

IgE

For the placebo group there was a steep increase from the pre-season to the on-season visit (Visit 4 to 5). For the Grazax group, this seasonal increase is blunted, and instead a gradual increase in IgE is observed until a plateau is reached at the on-season visit.

Figure 16: Study GT-12; Mean IgE antibody levels at different time points (FAS)



Source: Study GT-12 CSR Panel 9-28 (Figure 11 and Table 2.12)

7.3.2. Other efficacy studies Study P05239

7.3.2.1. Summary

A double blind, randomised, placebo controlled, parallel group study evaluating the efficacy and safety of sublingual immunotherapy with SCH 697243 (*Phleum pratense*) in children 5 to < 18 years of age with a history of grass pollen induced rhinoconjunctivitis with or without asthma.

Comment: The formulation for SCH 697243 is not provided in the CSR. The study was conduct by Schering Plough (owned by MSD). There is a statement that Grazax is the approved tradename in the EU, while in the US, the approved tradename is Grastek. With the exception of tradename, both products are identical. The original manufacturer (ALK) has a partnership with Merck Sharp & Dohme Corp whereby Merck have the rights to develop and commercialise Grastek in the USA

7.3.2.2. Study design, objectives, locations and dates

A randomised, double blind, placebo controlled, parallel group study conducted at 62 centres (52 in USA and 10 in Canada) from January 2008 to September 2009.

Primary objective

To evaluate the efficacy of the grass sublingual tablet (SCH 697243) versus placebo in the treatment of grass pollen induced rhinoconjunctivitis based on the total combined (sum of) rhinoconjunctivitis daily symptom score (DSS) and rhinoconjunctivitis daily medication score (DMS) averaged over the entire grass pollen season (GPS).

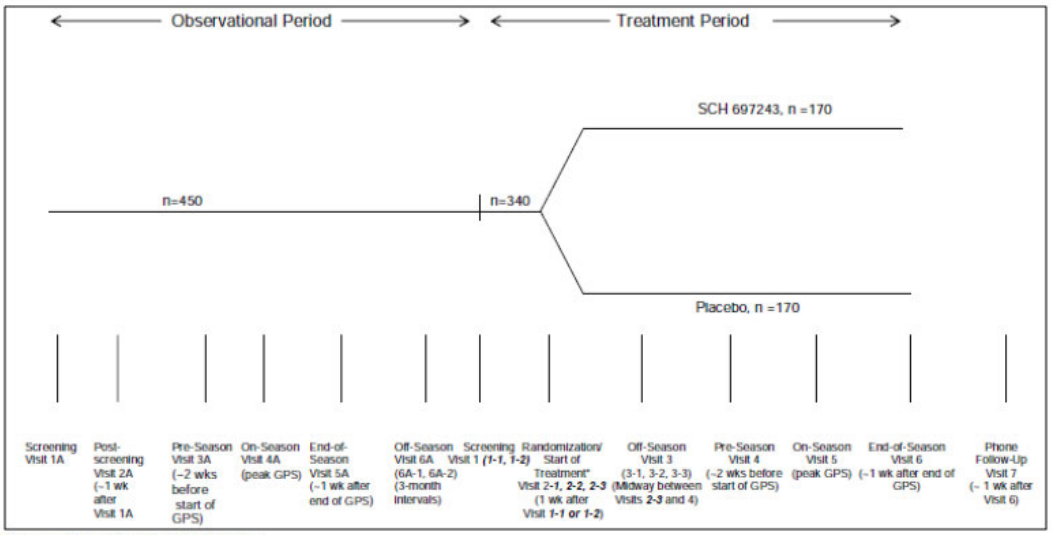
Secondary objectives

To assess overall safety and compare the following between the SCH 697243 and placebo groups:

1. The average rhinoconjunctivitis DSS for the entire GPS
2. The average rhinoconjunctivitis DMS for the entire GPS
3. The average weekly rhinoconjunctivitis quality of life total score for the entire GPS

This was an approximately 19 month study including an observational period during Year 1 2008 Grass Pollen Season (GPS) with no administration of investigational medicinal product (IMP), and a treatment period during Year 2 2009 GPS, with randomisation to either SCH 697243 or placebo. In the treatment period subjects the study consisted of at least 9 visits: Screening (2 visits), Randomisation (3 visits), Off-season, Pre-season, On-season, and End-of-season Visits, and at Unscheduled Visits as appropriate.

Figure 17: Study P05239; Study design



Source: Studs P05239 CSR Figure 1

7.3.2.3. Study population

Inclusion

Healthy male and female (non-childbearing potential) subjects aged 5 to < 18 years, with a clinical history of significant allergic rhinoconjunctivitis to grass (with or without asthma) and having received treatment during the previous GPS and with a positive SPT (average wheal ≥ 5 mm) and positive *Phleum pratense* specific IgE (≥ IgE Class 2) and FEV1 ≥ 70%.

Exclusion

Severe asthma; clinical history of symptomatic seasonal allergic and/or asthma to another allergen; significant symptomatic perennial allergic rhinitis and/or asthma requiring medication to an allergen to which the subject is regularly exposed; the subject did not experience an increase in rhinoconjunctivitis symptom score of equal to or greater than 4 above the pre-seasonal average symptom score for at least 2 days, and did not use allergy rescue medication for at least 2 days, during the observational period Year 1 2008 GPS.

7.3.2.4. Study treatments

At the start of the treatment period the subjects were randomised 1:1 using a computer generated randomisation schedule to either SCH697243 (Timothy grass AIT) or placebo. Study drugs were taken once daily in the morning for approximately 16 weeks prior to the GPS and during the GPS. The first 3 consecutive daily doses of the IMP were administered at the site, and the subjects were to be monitored for 30 minutes on site for observation of any AEs.

The study was double blind with the SCH 697243 and its matching placebo rapidly dissolving tablets being identical in appearance and packaging and similar in smell and taste.

Rescue medication

Rescue medication was provided for the study and given to the subjects as predefined, open label medication taken in a step wise fashion depending on the magnitude, severity, and type of symptoms.

Table 51: Study P05239; Schedule for rhinoconjunctivitis rescue medication

STEP	Rescue Medications	Subject Dosing Instruction	Requirements for Start of Use	Dispensed at Visits
1	Loratadine syrup (1 mg/mL) Loratadine 10 mg RediTabs tablet	5 mL QD for children 5 to <6 yr; 10 mL QD for children 6 to <18 yr 1 RediTabs tablet QD for children 6 to <18 yr	Total symptom score of ≥4 and start of GPS confirmed by site	3A, 4
1b	Olopatadine hydrochloride 0.1% ophthalmic solution	1 drop in each affected eye BID	In addition to loratadine for control of persistent eye symptoms	3A, 4
2	Mometasone furoate monohydrate nasal spray 50 mcg	1 spray in each nostril QD (ages 5 to <12 yr); 2 sprays in each nostril QD	Total symptom score of ≥4 despite loratadine. Use in addition to loratadine.	3A, 4
3	Prednisone tablet 5 mg (or prednisolone equivalent)	Day 1: 1 mg/kg/day (maximum 50 mg/day); Days 2, 3, 5, and 7: 0.5 mg/kg/day (maximum 25 mg/day)	Total symptom score of ≥4 despite loratadine and mometasone furoate monohydrate nasal spray. Use in addition to loratadine and mometasone furoate monohydrate nasal spray.	Unscheduled Visit [a]

QD = Once daily; BID = Twice daily; PRN = As needed; HFA = hydrofluoroalkane; GPS = Grass pollen season
a: To be dispensed only at Unscheduled Visits taking place after Visits 3A and 4. In countries where prednisone was not available, prednisolone was dispensed in a clinically equivalent dosage.
Source: Study P05239 CSR Table 4 (amended to include only rhinoconjunctivitis medications (Section 16.1.1.1)

7.3.2.5. Efficacy outcomes

Primary efficacy outcome

The total combined (sum of) rhinoconjunctivitis daily symptom score (DSS) and the rhinoconjunctivitis daily medication score (DMS) averaged over the entire grass pollen season (GPS).

Secondary outcomes:

- The average rhinoconjunctivitis DSS for the entire GPS
- The average rhinoconjunctivitis DMS for the entire GPS
- The average quality of life score for the PedRQLQ (6 to < 12 years) and the AdolRQLQ (12 to < 18 years) for the entire GPS
- The average rhinoconjunctivitis DSS for the peak GPS
- The average rhinoconjunctivitis DMS for the peak GPS
- The percentage of minimal symptom days for the entire GPS
- The average rhinoconjunctivitis DSS for the entire GPS and for the peak GPS by VAS
- The average asthma DSS and DMS for the entire GPS and for the peak GPS
- The Total Combined Score (TCS) at peak GPS

7.3.2.6. Statistical methods

For the observational period, the average DSS and DMS for the rhinoconjunctivitis and asthma symptoms for each subject were summarised.

The primary efficacy endpoint of combined (sum of) rhinoconjunctivitis DSS and DMS averaged over the entire GPS was evaluated using a linear model with asthma status, study site, and treatment group as fixed effects. This model was to allow for heterogeneous variance estimates

for each treatment group. For the primary endpoint, subjects with at least one post baseline diary record with DSS and DMS within the defined pollen season were included. The combined average score was based on all available data during the GPS for each subject. A 2-sided 95% CI of the difference in adjusted means (adjusted for asthma status, treatment, and study site) between the 2 treatment groups was presented. Also, the difference in adjusted means between the 2 treatment groups relative to the adjusted mean of the placebo group was presented as a percentage with corresponding confidence intervals.

The secondary endpoints were evaluated using a linear effect model with asthma status, treatment, and study site effects in the model. For the following key secondary endpoints, the type 1 error rate was controlled using the Hochberg's test:

1. SCH 697243 vs placebo on the average rhinoconjunctivitis DSS for the entire GPS.
2. SCH 697243 vs placebo on the average rhinoconjunctivitis DMS for the entire GPS.
3. SCH 697243 vs placebo on the average weekly rhinoconjunctivitis quality of life (RQLQ) total score for the entire GPS.

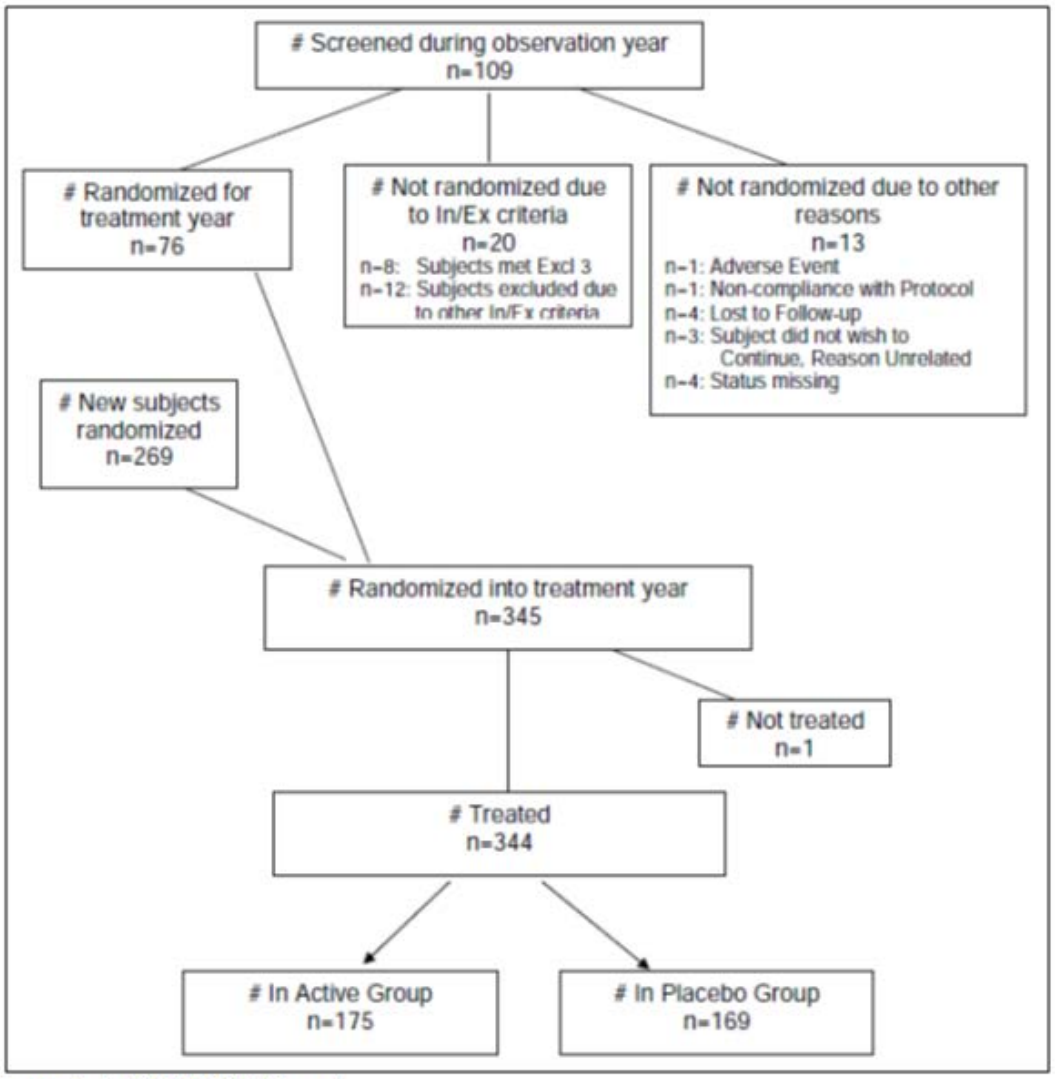
7.3.2.7. Sample size

In the observational period, up to 450 subjects were to be enrolled. Assuming a 25% dropout from the observational period, approximately 340 subjects were to be enrolled in the treatment period. New subjects were also to be enrolled after the start of the Year 1 2008 observational period GPS if needed to meet the targeted sample size. With approximately 170 subjects per group, the study was able to detect the following difference from placebo in the primary endpoint with 88% power at 5% level of significance (2-sided test):

- Differences of Effect (%) From Placebo to be Detected: 1.63 (23%)
- Estimate of Mean Placebo Effect: 7.07
- Estimate of Pooled Standard Deviation: 4.77

7.3.2.8. Participant flow

Figure 18: Study P05239; Participant flow



Source: Study P05239 CSR Figure 2

Table 52: Study P05239; disposition of subjects following randomised treatment assignment

Disposition of Subjects	Number (%) of Subjects		
	SCH 697243 (2800 BAU)	Placebo	Total
Treated	175 (100)	169 (100)	344 (100)
Discontinued Treatment Period	33 (19)	29 (17)	62 (18)
Adverse Event	13 (7)	5 (3)	18 (5)
Treatment Failure	0	1 (1)	1 (<1)
Lost to follow-up	4 (2)	0	4 (1)
Subject did not wish to continue for reasons unrelated to assigned study treatment	10 (6)	8 (5)	18 (5)
Noncompliance with protocol	5 (3)	14 (8)	19 (6)
Did not meet protocol eligibility	1 (1)	1 (1)	2 (1)
Completed Treatment Period	142 (81)	140 (83)	282 (82)

BAU = Bioequivalent Allergy Unit
Source: Study P05239 CSR Table 12 (Section 14.1.6)

7.3.2.9. Baseline data

A total of 344 subjects between 5 and < 18 years of age were randomised into the treatment period and received study drug. The 2 treatment groups were well-balanced regarding the baseline characteristics. The majority of subjects (61%) were between the ages of 12 and 18. An approximately equal percentage of subjects were male and female. The majority of subjects were White (88%), while 7% were Black or African American, 3% were multiracial, 2% were Asian, and 1% were Native Hawaiian or other Pacific Islander. Mean baseline heights and weights were similar between treatment groups. BMI was also similar between treatment groups, ranging from 13.5 to 48.8 kg/m^2 (mean of 20.48 kg/m^2 overall).

Tabulated data is provided in Section 18.7.

7.3.2.10. Results for the primary efficacy outcome

Total combined score (TCS)

Results of the TCS analysis showed a lower adjusted mean TCS for the SCH 697243 group (4.62) when compared with the placebo group (6.25) [difference = -1.63]. The difference in mean TCS was statistically significant (p = 0.001), and treatment with SCH 697243 provided a 26% improvement over treatment with placebo during the GPS.

Table 53: Study P05239: Summary and analysis of the total combined score (TCS) during the entire GPS (FAS)

	SCH 697243 2800 BAU (n=173)	Placebo (n=167)	Difference (%)	p-value	95% CI
Number of Subjects Included in Analysis	149	158			
Raw Mean(SD)	5.21 (4.68)	6.74 (4.80)			
Adjusted Mean(SE)	4.62 (0.52)	6.25 (0.51)	-1.63(-26%)	0.001	-2.60, -0.66
					(-38%, -10%)
Median	3.82	5.81			
Min, Max	(0.0, 22.66)	(0.0, 23.95)			
95% CI of the Mean	(4.45, 5.97)	(5.98, 7.49)			

SD=Standard Deviation, SE=Standard Error, CI=Confidence Interval, FAS=Full Analysis Set, BAU = Bioequivalent Allergy Unit, ANOVA = Analysis of Variance.
Endpoint Score range: TCS: 0-54 (sum of symptom and medication scores) % =Percent reduction in the 2800 BAU group compared to Placebo. Analysis via ANOVA with asthma status, treatment group, and site as fixed effects and adjusting for different error variation for each treatment group.
Source: Study P05239 CSR Table 18 (Section 14.2.1)

The SCH 697243 group had a statistically significantly lower mean TCS value compared to the placebo group during the preseason (defined as the last 14 days prior to GPS) (3.13 versus 4.52, respectively; p < 0.001).

Similar results were seen with the PP population.

7.3.2.11. Results for other efficacy outcomes

Rhinoconjunctivitis daily symptom score (DSS)

Analysis of the rhinoconjunctivitis DSS results during the entire GPS showed a lower adjusted mean DSS for the SCH 697243 group (3.71) compared to the placebo group (4.91). Treatment with SCH 697243 provided statistically significantly lower rhinoconjunctivitis symptoms (-25%; difference = -1.20; p = 0.005, adjusted for multiplicity) compared with placebo.

Table 54: Study P05239; Summary and analysis of the DSS during the entire GPS (FAS)

	SCH 697243 2800 BAU (n=173)	Placebo (n=167)	Difference (%)	p-value	Adjusted p-value	95% CI
Number of Subjects Included in Analysis	149	158				
Raw Mean (SD)	4.09 (3.50)	5.21 (3.76)				
Adjusted Mean (SE)	3.71 (0.40)	4.91 (0.41)	-1.20 (-25%)	0.002	0.005	-1.95, -0.45 (-36%, -9%)
Median	3.39	4.34				
Min - Max	(0.0, 14.22)	(0.0, 17.95)				
95% CI of the Mean	(3.53, 4.66)	(4.62, 5.81)				

SD = Standard Deviation, SE= Standard Error, CI= Confidence Interval, BAU = Bioequivalent Allergy Unit, ANOVA = Analysis of Variance, FAS = Full Analysis Set.
Adjusted p-values are based on Benjamini and Hochberg method.
Endpoint Score range: DSS: 0 - 18
% =Percent reduction in the 2800 BAU group compared to Placebo. Analysis via ANOVA with asthma status, treatment group, and site as fixed effects and adjusting for different error variation for each treatment group.
Source: Study P05239 CSR Table 19 (Section 14.2.6)

Average rhinoconjunctivitis DMS during GPS

Analysis of the rhinoconjunctivitis DMS results showed a lower adjusted mean DMS for the SCH 697243 group (0.91) compared to the placebo group (1.33); indicating the active drug group used less rescue medication for allergic rhinoconjunctivitis symptoms. Although the difference in medication score was 32% in favour of SCH 697243, the mean DMS for SCH 697243 was not significantly different from that of placebo (difference = -0.42; p = 0.066).

Table 55: Study P05239; Summary and analysis of the DMS during the entire grass pollen season (GPS) (FAS)

	SCH 697243 2800 BAU (n=173)	Placebo (n=167)	Difference (%)	p-value	adjusted p-value	95% CI
Number of Subjects Included in Analysis	149	158				
Raw Mean (SD)	1.11 (2.08)	1.52 (2.16)				
Adjusted Mean (SE)	0.91 (0.25)	1.33 (0.23)	-0.42 (-32%)	0.066	0.066	-0.88, 0.03 (-58%, 4%)
Median	0.12	0.64				
Min - Max	(0.0, 10.85)	(0.0, 11.08)				
95% CI of the Mean	(0.78, 1.45)	(1.18, 1.86)				

SD = Standard Deviation, SE= Standard Error, CI= Confidence Interval, BAU = Bioequivalent Allergy Unit, ANOVA = Analysis of Variance, FAS = Full Analysis Set.
Adjusted p-values are based on Benjamini and Hochberg method.
Endpoint Score range: DMS: 0 - 36
% =Percent reduction in the 2800 BAU group compared to Placebo. Analysis via ANOVA with asthma status, treatment group, and site as fixed effects and adjusting for different error variation for each treatment group.

The result was different in the PP subset analysis. In the PP subset, the SCH 697243 group had a lower adjusted mean rhinoconjunctivitis DMS (0.99) compared to the placebo group (1.50), a 34% reduction, and this difference was statistically significant (difference = -0.51; p = 0.044).

Average weekly rhinoconjunctivitis quality of life total score during GPS

The analysis of the average weekly RQLQ total score during the GPS showed a statistically significantly lower score for subjects treated with SCH 697243 compared to placebo (mean total scores of 1.45 and 1.77, respectively; p = 0.042, adjusted for multiplicity). Subjects treated with SCH 697243 demonstrated an 18% lower score over placebo. The difference in RQLQ demonstrated a statistically significant improvement in RQLQ for the grass AIT group, however, the RQLQ MID of 0.5 (considered clinically significant) was not obtained.

Table 56: Study P05239; Summary and analysis of RQLQ total score during GPS (FAS)

	SCH 697243 2800 BAU (n=173)	Placebo (n=167)	Difference (%)	p-value	Adjusted p-value	95% CI
Number of Subjects Included in Analysis	109	111				
Raw Mean (SD)	1.45 (1.11)	1.87 (1.17)				
Adjusted Mean (SE)	1.45 (0.11)	1.77 (0.12)	-0.32 (-18%)	0.028	0.042	-0.60, -0.03 (-32%, -2%)
Median	1.36	1.69				
Min - Max	(0.0, 4.91)	(0.0, 4.70)				
95% CI of the Mean	(1.24, 1.66)	(1.64, 2.09)				

SD = Standard Deviation, SE= Standard Error, CI= Confidence Interval, BAU = Bioequivalent Allergy Unit, FAS = Full Analysis Set, ANOVA = Analysis of Variance.
Adjusted p-values are based on Benjamini and Hochberg method.
Endpoint Score range: RQLQ Total Score: 0 – 6 (mean of all domain scores).
RQLQ total score during GPS is calculated as the average of weekly assessments during this period.
% =Percent reduction in the 2800 BAU group compared to Placebo. Analysis via ANOVA with asthma status, treatment group, and site as fixed effects and adjusting for different error variation for each treatment group.
Source: Study P05239 CSR Table 21 (Section 14.2.8)

When analysed during the peak GPS, the RQLQ total scores (evaluated on the FAS) achieved the MID (0.72) and showed statistically significantly lower total scores for SCH 697243 compared to placebo (1.19 active, 1.91 placebo; 38% difference [difference = -0.72]; p = 0.005), indicating that at the height of GPS, rhinoconjunctivitis quality of life is positively affected.

Table 57: Study P05239; Results for additional efficacy outcomes

Endpoint (FAS)	75,000 SQ-T (mean)	Placebo (mean)	p-value	Reduction (%)
Total combined score during peak GPS	4.73	6.85	<0.001	-31
Average rhinoconjunctivitis DSS during peak GPS	3.81	5.30	<0.001	-28
Average rhinoconjunctivitis DMS during peak GPS	0.92	1.55	0.049	-41
Number of minimal symptom days during entire GPS	18.7	11.23	<0.001	61
Percent of minimal symptom days during entire GPS	47.37	35.33	0.001	34
Average rhinoconjunctivitis DSS during entire GPS (VAS)	21.27	27.91	0.013	-23
Average rhinoconjunctivitis DSS during peak GPS (VAS)	22.97	30.44	0.007	-25%
Average asthma DSS during entire GPS	0.86	1.08	0.174	-21%
Average asthma DSS during peak GPS*	0.99	1.59		-38
Average asthma DMS during entire GPS	3.84	3.58	0.839	7
Average asthma DMS during peak GPS*	2.93	2.62		-19

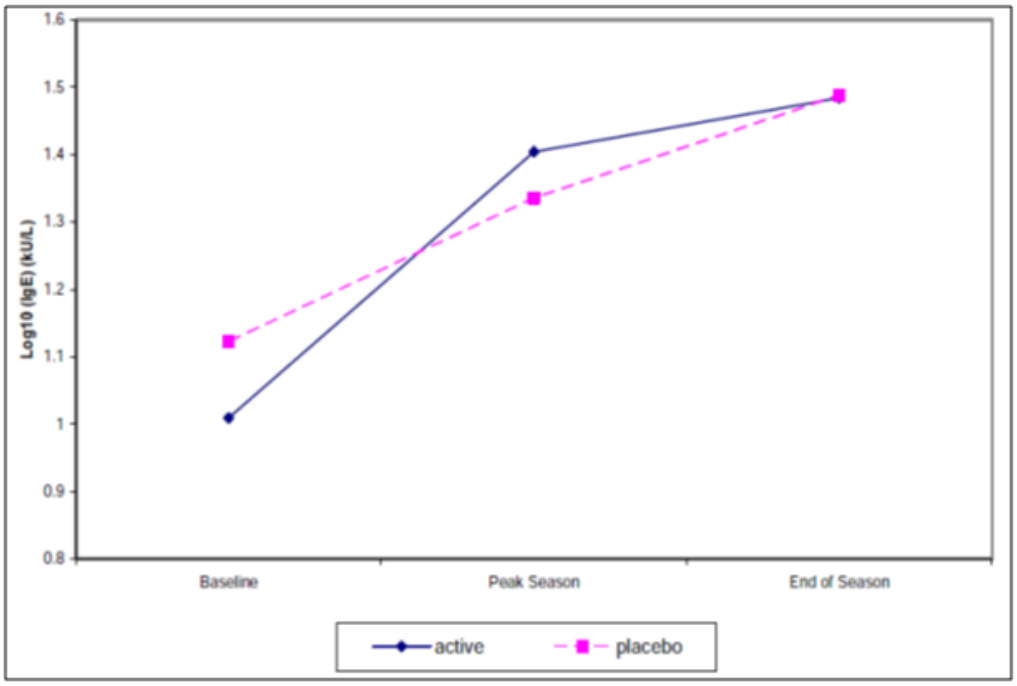
* numbers too small for statistical analysis
Source: Study P05239 CSR Tables 22-27 and Section 14.2.12 (Table 2.1.4.2 and 2.1.5.2) and Section 14.2.13.3 (Tables 2.1.4.3A and 2.1.4.4A)

Immunological results

Phleum pratense specific IgE

The results of the $\log_{10}$-transformed IgE values seen in the SCH 697243 group and in the placebo group were not statistically significant at peak season (1.20 and 1.12, respectively; p = 0.380) or at end-of-season, the $\log_{10}$-transformed IgE values (1.34 and 1.36, respectively, p = 0.860).

Figure 19: Study P05239: log_{10}(IgE) Immunological assessment over time (FAS)



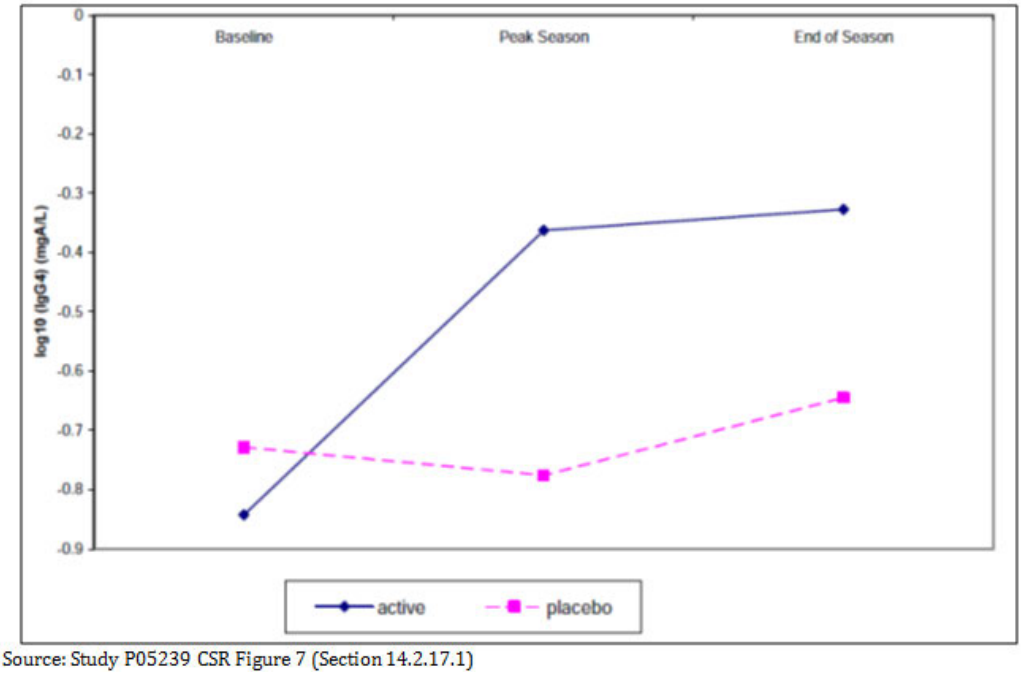
Source: Study P05239 CSR Figure 6 (Section 14.2.17.2.1)

Tabulated results were provided.

Phleum pratense specific IgG4

Higher log_{10}-transformed IgG4 values were seen in the SCH 697243 group than in the placebo group at both peak season and end-of-season ($p < 0.001$ for each). Induction of IgG4 antibodies may have an inhibitory role with respect to the IgE mediated response that results in allergic symptomology.

Figure 20: Study P05239: log_{10}(IgG4) Immunological assessment over time (FAS)



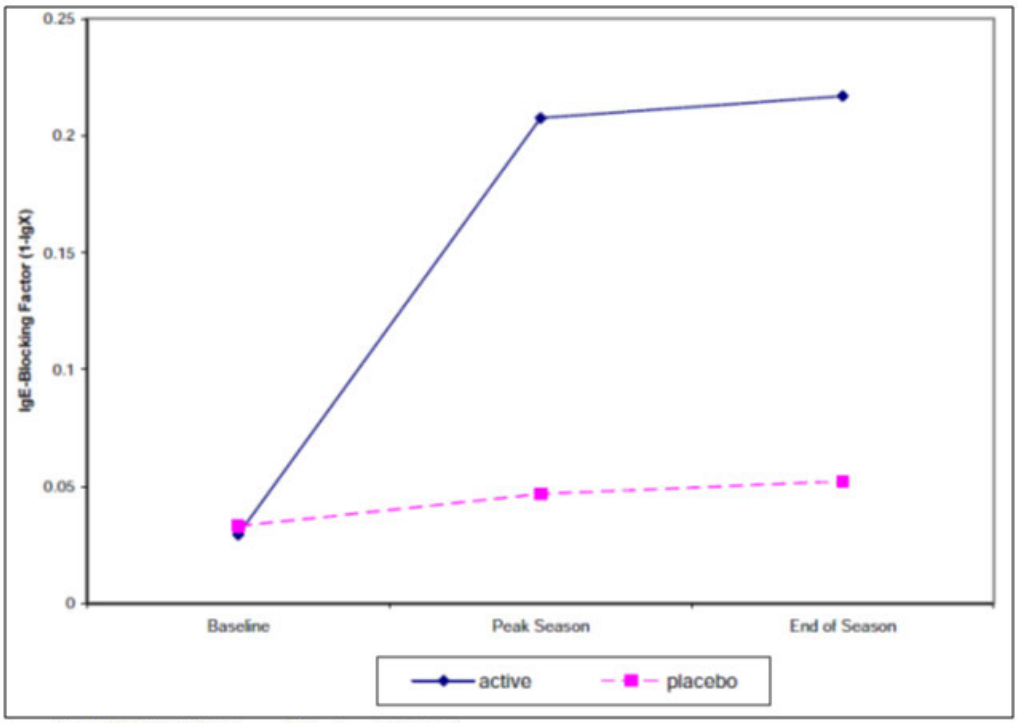
Source: Study P05239 CSR Figure 7 (Section 14.2.17.1)

Tabulated results are provided in Section 18.7.

Phleum pratense specific IgE-blocking factor

Higher IgE-blocking factor values were seen in the SCH 697243 group than in the placebo group at both peak season and end-of-season ($p < 0.001$ for each), indicating that SCH697243 induces the production of antibodies that interfere with allergen binding to IgE.

Figure 21: Study P05239; IgE-blocking factor over time (FAS)



Source: Study P05239 CSR Figure 8 (Section 14.2.17.1)

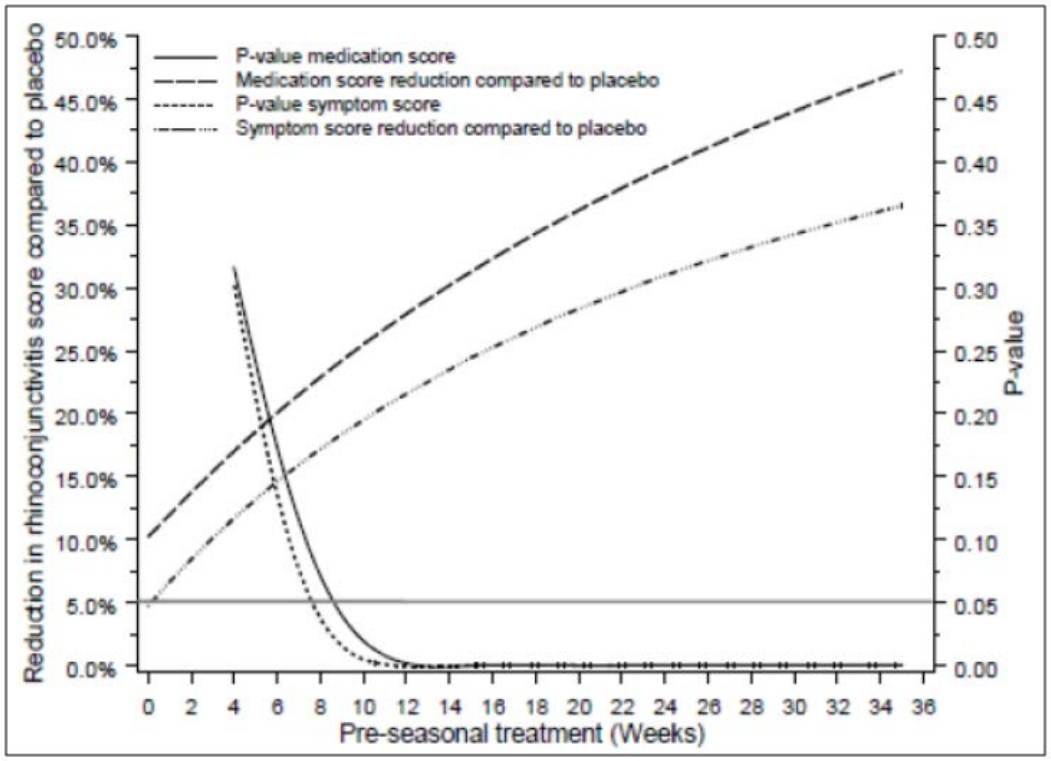
Tabulated results were provided.

7.3.3. Analyses performed across trials (pooled analyses and meta-analyses)

The sponsor did not provide any pooled analysis of the results, with the exception of a discussion of the length of time pre GPS was optimal for treatment.

The reduction in rhinoconjunctivitis symptom and medication score for patients receiving Grazax compared to placebo was estimated for 1, 2, 3,…, 24 weeks of pre-treatment (thus treatment effect at both 8 and 16 weeks of pre-treatment was estimated). In the Figure below the p-value for treatment difference (right y-axis) and the estimated reduction in rhinoconjunctivitis symptom and medication score compared to placebo (left y-axis) is shown.

Figure 22: Effect of Grazax pre-treatment duration on reduction in rhinoconjunctivitis symptom and medication score (GT-02, GT-07 and GT-08 1st GPS Combined)



From the figure it is evident that a statistically significant reduction in the average daily rhinoconjunctivitis symptom and medication score in the grass pollen season for patients treated with Grazax compared to patients treated with placebo was obtained with approximately 8 weeks of pre-treatment ($p < 0.05$). Further, it can also be derived that the symptom as well as the medication score was reduced by 17% to 23% after 8 weeks, which is considered to be clinically relevant. The reduction in the average daily rhinoconjunctivitis symptom and medication score increases with longer period of pre-treatment, which is reflected in the p-value approaching null.

7.4. Evaluator's conclusions on clinical efficacy for treatment of allergic rhinitis with or without conjunctivitis in adults and children

In the summary of clinical efficacy the sponsor identified 18 studies conducted with Grazax, of which 17 were included in the submission (Study PO8067 was not included). They identified 7 trials as supporting clinical efficacy; GT-02, GT-07, GT-08, GT-12, GT-14, P05238, and P05239. Of these studies GT-02, GT-07, GT-08, GT-14, P05238 were conducted in adults and GT-12, P05239 are in children. The sponsor does not identify any of the studies as pivotal and appears to give equal weight to all the studies and also makes little distinction between adults and children.

This evaluation has identified the adult studies GT-08 and GT-14 as pivotal studies based on having the same primary outcomes and the same formulation. The studies GT-07 and P05238 are considered supporting trials and GT-02 was primarily a dose finding study and therefore it was included (in this report). In children, Study GT-12 was considered pivotal as it had the same primary outcomes as the adult trials and P05239 was considered a supporting trial.

The trials had many varied outcome parameters and it is noted that most of the studies were conducted prior to the adoption of the EU Guidelines for treatment of allergic conditions but it is

reasonable to consider the guidelines in reviewing the data submitted as the studies generally comply to the guidelines and the sponsor makes reference to them at different times in the summaries.

In terms of the primary outcomes of the trials the EU guideline states:

> *Primary endpoint: The use of rescue medication has an impact on symptom severity. Therefore, the primary endpoint has to reflect both, symptom severity as well as the intake of rescue medication. ……. One approach is to combine both scores by a weighted sum of the symptom and medication score respectively. In such a situation the choice of the weights has to be justified.*

All of the trials have done this in some way but it differs in each trial; usually by using the co-primary endpoints of DSS and DMS or a combined endpoint (with no weighting) and then DSS and DMS as secondary endpoints.

The pivotal studies, GT-08 and GT-14 used DSS and DMS as the primary endpoint and then GT-08 added new secondary endpoints at each of the 4 subsequent years of the trial so that by the end of Year 5 there were 67 secondary outcomes. The EU guideline makes the point that:

"……..the applicant should provide a definition of a clinically meaningful effect in the primary efficacy endpoint and the basis for choosing this value. A merely statistical significant effect might not be sufficient." (EU Guideline on Treatment of Allergic Rhinoconjunctivitis)

While this guideline is not intended to apply to specific immunotherapy and refers to the primary endpoint, the point is a good one and there is danger that using so many secondary endpoints raises concern regarding selective selection of the data.

Looking at the primary (or key secondary) outcomes in the efficacy studies.The evaluator has noted a lack of critical discussion of results in the individual study reports and summaries. This has limited the ability to comment on consistent efficacy, that the sponsor has claimed. The results of the efficacy studies for the entire GPS are as shown in Table 58.

Table 58; results of the efficacy studies for the entire GPS

Study	DSS		DMS		Combined Score	
Adults	**% Reduction**	**p-value**	**% reduction**	**p-value**	**% reduction**	**p-value**
GT-08 year 1	31	<0.0001	39	<0.0001		
GT-14	6.2	0.3475	27	0.0827		
GT-02	16	0.071	28	0.047*		
GT-07	25	0.0503	32	0.136		
P05238	18	0.005	26	0.084	20	0.005
Children						
GT-12	22	0.0215	34	0.0156		
P05239	25	0.002	32	0.066	26	0.001

* Significance could not be claimed due to hierarchical structure of testing procedure.

When viewing the results in this way the studies do not show a consistent benefit as claimed by the sponsor. For adults only 2 of 5 studies show statistically significant benefit for rhinoconjunctivitis symptoms and only 1 of 5 show statistically significant benefit for DMS.

The sponsor argues that the reasons the primary analysis in studies GT-02 and GT-14 did not show a statistically significant difference compared to placebo was due, to the fact that, in Study GT-02, not all subjects were able to comply with the 8 week pre-seasonal treatment period and in Study GT-14 to the subjects' pre-seasonal symptom score, overlapping pollen seasons/allergies and/or geographical regions/pollen areas. These may be valid reasons for these studies but also reflect the real world use of the product.

The question is then how much efficacy is required to register the product? Normally, efficacy in 2 independent trials or 1 study with significant and clinically relevant results is considered

sufficient for acceptance of a product's efficacy. Grazax meets these criteria and therefore is recommended for approval for the indication of treatment of allergic rhinitis with or without conjunctivitis.

The sponsor is also seeking an indication of disease modifying. It is noted that this was granted in the EU but not in the USA. The EU guideline does not provide much guidance as what evidence is required for a disease modifying claim, the only guidance is that for long-term efficacy and disease modifying effect a "sustained significant and clinically relevant efficacy in post treatment years" is required (EU guideline on Treatment of allergic diseases).

Only 1 study investigated the long term effect of Grazax, so the disease modifying claim rests with Study GT-08 that treated patients for 3 years and then followed them for 2 years. A sustained significant and clinically relevant effect was seen for the firstbut not the second year (the rhinoconjunctivitis medication score was not statistically significant). The sponsor argues that the second year (2009) grass pollen season was significantly milder than the previous seasons and due to the confirmed influence of grass pollen exposure on the symptom and medication scores, this was inevitably influencing the size of the efficacy measurements. However, whatever the reason, the sustained benefit was not present in the second year of follow up. This plus the variability seen in the other trials, is not sufficient for a claim of disease modifying.

It is noted that the wording of the requested indication is for "grass pollen" allergy without specifying *Phleum pratense*. This should be included in the indication to reflect the studies submitted.

It is recommended that the product be approved but for the amended indication:

> *Grazax is indicated for treatment of Timothy grass (Phleum pratense) pollen allergic rhinitis with or without conjunctivitis in adults, adolescents and children (above the age of 5) with clinically relevant symptoms, confirmed by a positive cutaneous test and/or a positive titre of the specific IgE to Phleum pratense.*

8. Clinical safety

Comment: The Summary of Clinical Safety was inadequate since it did not provide an integrated analysis of safety data. Moreover, it did not consist of the required elements. Safety data was also noted to be reported in the Clinical Overview and RMP and hence limiting the ability to perform a comprehensive safety assessment.

8.1. Studies providing evaluable safety data

The following studies provided evaluable safety data:

Pivotal efficacy studies; GT-08, GT-14 and GT-12

In the pivotal efficacy studies, the following safety data were collected:

- General adverse events (AEs) were assessed by recording all AEs reported by the subjects and also which were not spontaneously reported by the subject, but were elicited by asking a non-leading question such as "How are you feeling?"
- AEs of particular interest were not identified
- Laboratory tests, including routine haematology, blood chemistry and urinalysis were performed at baseline and at end of treatment (approximately 1 week after end of GPS) and any unscheduled visits
- Vital signs (blood pressure and heart rate) and physical examination including the standard questioning and tests (general appearance, head (oral inspection, ears, eyes, nose and

throat), respiratory [auscultation/stethoscopy examination of the lungs], heart [auscultation/stethoscopy of the heart], lymph nodes and skin) was performed at baseline and at end of treatment (approximately 1 week after end of GPS) and any unscheduled visits

- FEV1 was performed at baseline and at end of treatment (approximately 1 week after end of GPS) and any unscheduled visits

8.1.1. Pivotal studies that assessed safety as a primary outcome

Not applicable.

8.1.2. Dose response and non-pivotal efficacy studies

The dose response and non-pivotal efficacy studies provided safety data, as follows:

Adults

Study GT-01 provided data on the occurrence of AEs including SAEs and the occurrence of pre-defined symptoms (local allergic reactions in or around the mouth, runny nose, sneezing, itching nose, flushing of face, urticaria, asthma and difficulty in breathing, nausea, diarrhoea, stomach ache, rumbling in the stomach, tiredness, and headache).

Study GT-02 provided data on the occurrence of AEs, including SAE and AEs leading to withdrawal, vital signs (blood pressure, heart rate and auscultation/stethoscopy examination of the lungs), 12-lead ECG, physical examination (including an oral inspection), standard clinical laboratory tests and spirometry (FEV1).

Study GT-03 provided data on the occurrence of AEs, physical examination, oral examination, vital signs, 12-lead ECG, standard clinical laboratory tests and concomitant medication.

Study GT-04 provided data on the occurrence of AEs, physical examination, oral examination, vital signs, 12-lead ECG, standard clinical laboratory tests, concomitant medication and lung function.

Study GT-07 provided data on asthma symptom score and the use of asthma rescue medication during the grass pollen season, and prior to the start of the grass pollen season. Further safety endpoints included AEs, SAEs, lung function, heart function, haematology, blood chemistry, urine values, vital signs and physical examinations.

Study GT-10 and GT-17 provided data on AEs and SAEs.

Study GT-16 provided data on all AEs and SAEs, findings from physical examinations and vital signs.

Study GT-19 provided data on all AEs and SAEs, oral examination, physical examination, vital signs, and FEV1.

Study P05238 provided data on all AEs, vital signs, physical examinations, ECGs (screening only), pulmonary function tests, examination of oral cavity, and safety laboratory assessments.

Children

Study GT-09 and GT-11 provided data on AEs, clinical safety laboratory tests, vital signs, physical examinations and oral examination.

Study GT-P05239 provided data on all AEs, vital signs, physical examinations, ECGs (screening only), pulmonary function tests, examination of oral cavity, and safety laboratory assessments.

8.1.3. Other studies evaluable for safety only

Studies GT-10 and GT-17 evaluated a compliance device which is not intended for use in Australia.

8.1.3.1. Clinical pharmacology studies

A summary of Study GT-18 was provided. Safety assessment was similar to efficacy studies.

8.2. Patient exposure

Table 59: Patient exposure by dose

Total population	
Dose of exposure	**Number of subjects**
Active 2,500 SQ-T	154
Active 25,000 SQ-T	169
Active 75,000 SQ-T	**2482**
Active 125,000 SQ-T	9
Active 150,000 SQ-T	18
Active 300,000 SQ-T	18
Active 375,000 SQ-T	7
Active 500,000 SQ-T	14
Active 750,000 SQ-T	9
Active 1,000,000 SQ-T	9
Total unique subjects*	**2864**

The table is based on exposure to GRAZAX in trials: GT-01, GT-The table is based on exposure to GRAZAX in trials: GT-01, GT-02, GT-03, GT-04, GT-07, GT-08 + Extension, GT-09, GT-10 + Extension, GT-11, GT-12, GT-14, GT-16, GT-17, GT-18, GT-19, P05238, and P05239.
* Unique subject exposed to at least one dose
Source: Module 2.5 Table 7

Table 60: Extent of exposure to Grazax by duration

Exposure by duration	Number of subjects*
< 4 weeks	197
[4 weeks; 12 weeks]	332
[12 weeks; 24 weeks]	614
≥ 24 weeks	1325
Missing duration	14

The table is based on exposure to GRAZAX in trials: GT-01, GT-02, GT-03, GT-04, GT-07, GT-08 + Extension, GT-09, GT-10 + Extension, GT-11, GT-12, GT-14, GT-16, GT-17, GT-18, GT-19, P05238, and P05239.
Source: Module 2.5 Table 8

Table 61: Exposure to 75,000 SQ-T by age group and gender

	Number of subjects			
Age	**Male**	**Female**	**Sex unknown**	**Total**
≤17	323	168	-	491
>17	1,446	1,289	2	2,737
Age unknown	5	2	-	7
Total	**1,774**	**1,459**	**2**	**3,235**

The table is based on exposure to GRAZAX in trials: GT-01, GT-02, GT-03, GT-04, GT-07, GT-08 + Extension, GT-09, GT-10 + Extension, GT-11, GT-12, GT-14, GT-16, GT-17, GT-18, GT-19, P05238, P05239, and P08067 (not included in submission).
Source: RMP Table 7

Table 62: Exposure to 75,000 SQ-T by ethnic or racial origin

Total population	
Ethnic/racial origin	**Number of subjects**
African	12
Asian	73
Asian or Pacific Islander	11
Black or African American	128
Black, not Hispanic origin	8
Caucasian	1,573
Hispanic	8
Hispanic or Latino	4
Latin American	4
Multiracial	29
Native Hawaiian or Other Pacific Islander	4
Other	15
White	1,082
White, not of Hispanic origin	272
American Indian or Alaskan Native	6
Race unknown	6
Total	**3,235**

The table is based on exposure to GRAZAX in trials: GT-01, GT-02, GT-03, GT-04, GT-07, GT-08 + Extension, GT-09, GT-10 + Extension, GT-11, GT-12, GT-14, GT-16, GT-17, GT-18, GT-19, P05238, P05239, and P08067 (not included in submission).
Source: RMP Table 8

Comment: No explanation is provided to explain the reason for listing both "Caucasian" and "White" but it appears to be a mix of the FDA and ICH M4E eCTD definitions, where the studies were conducted and the lack of integration by the sponsor.

8.3. Adverse events

8.3.1. All adverse events (irrespective of relationship to study treatment)

Overall, the majority of subjects in all trials experienced at least 1 AE. The data show that there was more AEs in the active immunotherapy groups when compared with placebo.

8.3.1.1. Pivotal studies

Adults

Study GT-08

265 (84%) subjects treated with 75,000 SQ-T and 205 (64%) treated with placebo reported at least 1 AE during the first year. The majority of the most frequently reported AEs during the first year were application site related indicating drug relationship, for example oral pruritus was reported by 46% of actively treated subjects versus 4% of placebo treated subjects. For other AEs no differences between treatment groups were seen for example headache, nasopharyngitis and influenza were equally reported in both groups.

Table 63: Study GT-08 TEAEs reported by ≥ 5% of subjects in first year

Treatment Group	75,000 SQ-T			Placebo			Overall		
	N	(%)	E	N	(%)	E	N	(%)	E
number of subjects	316			318			634		
all adverse events	265	(84)	824	205	(64)	507	470	(74)	1331
oral pruritus	145	(46)		13	(4)		158	(25)	191
nasopharyngitis	47	(15)		60	(19)		107	(17)	151
oedema mouth	58	(18)		2	(1)		60	(9)	70
influenza	23	(7)		24	(8)		47	(7)	53
ear pruritus	38	(12)		3	(1)		41	(6)	42
throat irritation	30	(9)		3	(1)		33	(5)	37
headache	9	(3)		19	(6)		28	(4)	44

N = Number of subjects, % = Percent of subjects, E = Number of events,
Source: Study GT-08 CSR Table 10-2 (EOT Table 3.1)

During the extension of the trial, the numbers of AEs in the active group approached that of the placebo group.

Study GT-14

121 of 163 subjects (74%) treated with Grazax and 101 of 166 subjects (61%) treated with placebo reported at least 1 AE during the trial. All frequently reported AEs related to IMP were local reactions in ear, mouth or throat (ear pruritus, mouth oedema, oral pruritus, oral paraesthesia and throat irritation). The majority of the IMP related AEs were reported by subjects treated with Grazax. The most frequently reported AE considered related to IMP was oral pruritus (17% of subjects in the Grazax group; < 1% in the placebo group).

Table 64: Study GT-14: All TEAE reported by ≥ 5% of subjects (FAS)

	Placebo			Grazax		
	N	%	E	N	%	E
Number of subjects	**166**			**163**		
Ear and Labyrinth Disorders						
Ear pruritus	1	<1	1	16	10	18
Gastrointestinal Disorders						
Oedema mouth	-	-	-	9	6	9
Oral pruritus	1	<1	1	29	18	32
Infections and Infestations						
Nasopharyngitis	24	14	26	23	14	25
Sinusitis	6	4	6	12	7	14
Upper respiratory tract infections	15	9	18	17	10	23
Nervous System Disorders						
Headache	12	7	19	8	5	10
Paraesthesia oral	2	1	2	14	9	16
Respiratory, Thoracic and Mediastinal						
Throat irritation	4	2	4	24	15	27
Skin and Subcutaneous Tissue Disorders						
Urticaria	-	-	-	8	5	9

N = Number of subjects; % = Percent of subjects of FAS (all randomised subjects); E = Number of events
Source: Study GT-14 CSR Panel 10-2 (Table 4.1)

Children

Study GT-12

109 (87%) subjects in the Grazax group and 106 (83%) in the placebo group reported at least 1 AE.

Table 65: Study GT-12: Summary of all TEAE occurring in ≥ 5% patients

	Placebo			Grazax		
	N	%	E	N	%	E
Patients with asthma symptoms						
Number of subjects	**90**			**78**		
All AEs	**78**	**87**	**217**	**68**	**87**	**259**
Eye Disorders	9	10	10	12	15	17
Conjunctivitis	6	7	6	4	5	4
Conjunctivitis allergic	0	0	0	5	6	5
Eye pruritus	3	3	3	4	5	5
Gastrointestinal disorders	11	12	12	27	35	37
Oral pruritus	3	3	3	19	24	22
Vomiting	1	1	1	4	5	4
Infections and infestations	48	53	83	48	62	83
Bronchitis	5	6	5	2	3	2
Nasopharyngitis	6	7	6	12	15	12
Otitis media	6	7	6	3	4	4
Tonsillitis	3	3	3	4	5	4
Upper respiratory tract infection	8	9	15	7	9	8
Viral infection	9	10	10	16	21	18
Injury, poisoning and procedural complications	10	11	10	8	10	9
Contusion	0	0	0	4	5	4
Neoplasms benign, malignant and unspecified	3	3	3	4	5	4
Skin papilloma	3	3	3	4	5	4
Nervous system disorders	6	7	6	7	9	8
Headache	6	7	6	3	4	3
Respiratory, thoracic and mediastinal disorders	37	41	63	28	36	46
Asthma	11	12	13	4	5	8
Cough	11	12	14	4	5	5
Dyspnoea	5	6	8	5	6	5
Throat irritation	1	1	1	8	10	8
Patients without asthma						
Number of subjects	**31**			**39**		
All AEs	**25**	**81**	**52**	**34**	**87**	**136**
Eye Disorders	2	6	2	7	18	8
Conjunctivitis	1	3	1	2	5	2
Conjunctivitis allergic	0	0	0	2	5	2
Lip swelling	0	0	0	2	5	2
Gastrointestinal disorders	2	6	2	23	59	32
Abdominal pain	0	0	0	2	5	2
Diarrhoea	1	3	1	2	5	2
Lip blister	0	0	0	2	5	2
Oral pruritus	0	0	0	17	44	20
Vomiting	1	3	1	2	5	2
Infections and infestations	15	48	21	25	64	47
Influenza	1	3	1	5	13	5
Nasopharyngitis	0	0	0	5	13	5
Otitis media	0	0	0	4	10	4
Upper respiratory tract infection	3	10	3	4	10	5
Viral infection	4	13	4	8	21	8
Injury, poisoning and procedural complications	3	10	3	6	15	6
Arthropod bite	1	3	1	2	5	2
Joint sprain	1	3	1	2	5	2
Neoplasms benign, malignant and unspecified	1	3	1	2	5	2
Skin papilloma	1	3	1	2	5	2
Nervous system disorders	2	6	3	3	8	3
Headache	2	6	3	1	3	1
Paraesthesia oral	0	0	0	2	5	2
Respiratory, thoracic and mediastinal disorders	11	35	11	14	36	18
Cough	3	10	3	4	10	4
Nasal passage irritation	2	6	2	0	0	0
Throat irritation	0	0	0	4	10	4

8.3.1.2. Other studies

Adults

Study GT-07

93% of the subjects reported AEs with the percentage slightly higher in the active treatment group. The most frequently reported AEs were oral pruritus nasopharyngitis and throat irritation.

Table 66: Study GT-07, AEs reported by ≥ 5% of subjects

System Organ Class Preferred Term	Placebo (N=40)			75,000 SQ-T (N=74)			Overall (N=114)		
	N	%	E	N	%	E	N	%	E
Ear and labyrinth disorders									
Ear pruritus	0			14	19	14	14	12	14
Eye disorders									
Eye pruritus	1	3	2	5	7	7	6	5	9
Gastrointestinal disorders									
Diarrhoea	2	5	2	3	4	6	5	4	8
Glossitis		0		5	7	7	5	4	7
Nausea	3	8	6	4	5	4	7	6	10
Oedema mouth	1	3	1	11	15	12	12	11	13
Oral pruritus	2	5	3	39	53	56	41	36	59
General disorders and administration site conditions									
Fatigue	5	13	5	8	11	9	13	11	14
Immune system disorders									
Seasonal allergy	3	8	3	5	7	5	8	7	8
Infections and infestations									
Influenza	4	10	4	5	7	5	9	8	9
Nasopharyngitis	10	25	13	27	36	38	37	32	51
Nervous system disorders									
Headache	5	13	9	13	18	23	18	16	32
Respiratory, thoracic and mediastinal disorders									
Asthma	4	10	5	8	11	10	12	11	15
Cough	2	5	2	6	8	7	8	7	9
Dyspnoea	2	5	2	0			2	2	2
Epistaxis	2	5	2	0			2	2	2
Nasal congestion	2	5	4	6	8	7	8	7	11
Nasal passage irritation	2	5	5	4	5	4	6	5	9
Oropharyngeal swelling	0			6	8	10	6	5	10
Pharyngolaryngeal pain	2	5	2	6	8	9	8	7	11
Rinorrhoea	2	5	2	4	5	4	6	5	6
Sneezing	1	3	1	5	7	5	6	5	6
Throat irritation	3	8	3	24	32	28	27	24	31

N=number of subjects; %=percent of subjects having the event; E=number of events
Source: Module 2.7.4 Table 41 (Study GT-07 CSR Table 10-4)

Study P05238

77% of subjects reported an AE during the treatment period; 83% in the Grazax group and 72% in the placebo group. The most commonly reported AEs in the Grazax group were oral pruritus, throat irritation, upper respiratory tract infection, nasopharyngitis, and ear pruritus.

Table 67: Study P05238: Summary of AEs during the treatment period reported by ≥ 5% of subjects in either treatment group (all treated subjects)

	Number (%) of Subjects		
	SCH 697243 2800 BAU (n=213)	Placebo (n=225)	Total (N=438)
Subjects Reporting Any Adverse Event	176 (82.6)	161 (71.6)	337 (76.9)
Ear and Labyrinth Disorders			
Ear Pruritus	42 (19.7)	3 (1.3)	45 (10.3)
Eye Disorders			
Eye Pruritus	11 (5.2)	8 (3.6)	19 (4.3)
Gastrointestinal Disorders			
Dyspepsia	11 (5.2)	3 (1.3)	14 (3.2)
Oedema Mouth	17 (8.0)	1 (0.4)	18 (4.1)
Oral Pruritus	75 (35.2)	7 (3.1)	82 (18.7)
Paraesthesia Oral	29 (13.6)	5 (2.2)	34 (7.8)
Stomatitis	16 (7.5)	1 (0.4)	17 (3.9)
Swollen Tongue	11 (5.2)	0	11 (2.5)
Infections and Infestations			
Nasopharyngitis	17 (8.0)	29 (12.9)	46 (10.5)
Upper Respiratory Tract Infection	38 (17.8)	25 (11.1)	63 (14.4)
Nervous System Disorders			
Headache	15 (7.0)	16 (7.1)	31 (7.1)
Respiratory, Thoracic and Mediastinal Disorders			
Pharyngeal Oedema	14 (6.6)	0	14 (3.2)
Throat Irritation	63 (29.6)	11 (4.9)	74 (16.9)
Skin and Subcutaneous Tissue Disorders			
Pruritus	11 (5.2)	6 (2.7)	17 (3.9)

BAU = Bioequivalent Allergy Unit
Source: Study P05238 CSR Table 36 (Sections 14.3.1.1 and 14.3.1.1.1) (amended to include only AEs ≥5%)

Children

Study P05239

Overall, 82% (282/344) of subjects reported an AE during the treatment period. The occurrence of all AEs was 86.3% in the SCH 697243 group and 77.5% in the placebo group. The most commonly reported AEs were oral pruritus and throat irritation with other frequently occurring AEs including nasopharyngitis, upper respiratory tract infection and oropharyngeal.

Table 68: Study P05239: Summary of AEs during the treatment period reported by ≥ 5% of subjects in either treatment group (all treated subjects)

	Number (%) of Subjects		
	SCH 697243 2800 BAU (n=175)	Placebo (n=169)	Total (N=344)
Subjects Reporting Any Adverse Event	151 (86.3)	131 (77.5)	282 (82.0)
Ear and Labyrinth Disorders			
Ear Pruritus	21 (12.0	1 (0.6)	22 (6.4)
Eye Disorders			
Eye Pruritus	15 (8.6)	4 (2.4)	19 (5.5)
Gastrointestinal Disorders			
Lip Swelling	13 (7.4)	0	13 (3.8)
Oedema Mouth	19 (10.9)	1 (0.6)	20 (5.8)
Oral Pruritus	68 (38.9)	6 (3.6)	74 (21.5)
Stomatitis	26 (14.9)	2 (1.2)	28 (8.1)
General Disorders and Administration Site Conditions			
Pyrexia	9 (5.1)	12 (7.1)	21 (6.1)
Infections and Infestations			
Influenza	6 (3.4)	9 (5.3)	15 (4.4)
Nasopharyngitis	26 (14.9)	32 (18.9)	58 (16.9)
Sinusitis	5 (2.9)	9 (5.3)	14 (4.1)
Upper Respiratory Tract Infection	21 (12.0)	22 (13.0)	43 (12.5)
Viral Upper Respiratory Tract Infection	11 (6.3)	12 (7.1)	23 (6.7)
Nervous System Disorders			
Headache	19 (10.9)	20 (11.8)	39 (11.3)
Respiratory, Thoracic and Mediastinal Disorders			
Cough	16 (9.1)	19 (11.2)	35 (10.2)
Nasal Congestion	11 (6.3)	8 (4.7)	19 (5.5)
Oropharyngeal Pain	23 (13.1)	19 (11.2)	42 (12.2)
Pharyngeal Erythema	13 (7.4)	3 (1.8)	16 (4.7)
Sneezing	9 (5.1)	2 (1.2)	11 (3.2)
Throat Irritation	65 (37.1)	5 (3.0)	70 (20.3)

BAU = Bioequivalent Allergy Unit
Source: Study P05239 CSR Table 36 (Sections 14.3.1.1 and 14.3.1.1.1) (amended to include only AEs ≥5%)

8.3.1.3. Other studies

The results were similar in the other studies which were provided.

8.3.2. Treatment-related adverse events (adverse drug reactions)

Overall, 57% of subjects receiving Grazax reported treatment related AEs. These AEs were primarily reported during the first 3 months of treatment (56% reported AEs within the first 3 months of treatment).

Oral pruritus was the most frequently reported related AE, experienced by 30% of the subjects treated with Grazax. Throat irritation, oedema mouth and ear pruritus were also frequently reported (by 8 to 16% of the subjects treated with Grazax).

Table 69: Treatment related AEs reported by ≥ 2% of Subjects

System Organ Class Preferred Term	Grazax N=2482 n (%) e	Placebo N=1486 n (%) e
All related TEAE	1413 (57%) 5077	384 (26%) 864
Ear and labyrinth disorders		
Ear pruritus	222 (9%) 316	17 (1%) 29
Eye disorders		
Eye pruritus	74 (3%) 106	36 (2%) 44
Gastrointestinal disorders		
Lip swelling	83 (3%) 112	3 (<1%) 3
Oedema mouth	202 (8%) 289	9 (1%) 9
Oral discomfort	41 (2%) 44	6 (<1%) 10
Oral pruritus	755 (30%) 1307	79 (5%) 111
Paraesthesia oral	123 (5%) 175	20 (1%) 22
Stomatitis	67 (3%) 111	8 (1%) 9
Swollen tongue	39 (2%) 47	1 (<1%) 1
Nervous system disorders		
Headache	42 (2%) 59	17 (1%) 22
Respiratory, thoracic and mediastinal disorders		
Cough	48 (2%) 69	19 (1%) 22
Oropharyngeal pain	50 (2%) 76	23 (2%) 26
Pharyngeal oedema	63 (3%) 103	3 (<1%) 3
Sneezing	41 (2%) 56	25 (2%) 29
Throat irritation	401 (16%) 719	44 (3%) 59
Skin and subcutaneous tissue disorders		
Pruritus	32 (1%) 45	23 (2%) 32
Grazax Adult Trials		
All related TEAE	1189 (56%) 3431	299 (25%) 695
Grazax Paediatric Trials		
All related TEAE	224 (65%) 1646	85 (27%) 169

System organ class and preferred term is coded in MedDRA version 12.1; related are all events that are not "unlikely", not "unrelated" or "not related"; N=number of randomised subjects in the Grazax trials below; n=number of subjects having a related TEAE in the Grazax trials below; %=percent of all randomised subjects; e=number of events.
GT-01: 20 subjects received 75,000 SQ-T and 25 received placebo (Periods 1 to 4); **GT-02**: 294 subjects received 75,000 SQ-T (Groups 4 and 6) and 286 received placebo (Groups 1 and 5); **GT-03**: 9 subjects received 75,000 SQ-T and 21 subjects received placebo; **GT-04**: 9 subjects received 75,000 SQ-T and 11 subjects received placebo; **GT-07**: 74 subjects received 75,000 SQ-T and 40 received placebo; **GT-08**: 316 subjects received 75,000 SQ-T and 318 received placebo; **GT-09**: 23 subjects received 75,000 SQ-T and 7 received placebo; **GT-10**: 460 subjects received 75,000 SQ-T; **GT-11**: 22 subjects received 75,000 SQ-T and 8 received placebo; **GT-12**: 126 subjects received 75,000 SQ-T and 127 received placebo; GT-14: 163 subjects received 75,000 SQ-T and 166 received placebo; **GT-16**: 52 subjects received 75,000 SQ-T and 26 received placebo; **GT-17**: 261 subjects received 75,000 SQ-T; **GT-18**: 219 subjects received 75,000 SQ-T and 57 received placebo; **GT-19**: 46 subjects received 75,000 SQ-T; **P05238**: 213 subjects received 75,000 SQ-T and 225 received placebo; **P05239**: 175 subjects received 75,000 SQ-T and 169 received placebo.
Source: Module 2.7.4 Table 59

8.3.2.1. AEs in children compared to adults

56% of adults and 65% of children/adolescents receiving Grazax reported treatment related AEs (test for difference: odds ratio = 0.68; CI95 [0.54-0.87]; p = 0.002). The AE profile in children/adolescents treated with Grazax was similar to that observed in adults.

Table 70: Frequency differences based on all AEs between children/adolescents and adults treated with Grazax (p ≤0.05)

System Organ Class Preferred Term	Children /Adolescents N=346 n (%) e	Adults N=2136 n (%) e
Blood and lymphatic system disorders		
Lymphadenopathy	3 (0.9) 3	3 (0.1) 4
Eye disorders		
Eye pruritus	25 (7.2) 36	68 (3.2) 100
Conjunctivitis [1]	20 (5.8) 30	69 (3.2) 74
Conjunctivitis hyperaemia [2]	11 (3.2) 15	12 (0.6) 13
Ear and labyrinth disorders		
Ear discomfit [3]	8 (2.3) 8	15 (0.7) 19
Gastrointestinal disorders		
Abdominal pain [4]	25 (7.2) 51	76 (3.6) 87
Dysphagia	8 (2.3) 11	19 (0.9) 25
Oral soft tissue conditions [5]	6 (1.7) 7	12 (0.6) 14
Lip blister [6]	7 (2.0) 9	16 (0.7) 20
Lip swelling [7]	32 (9.2) 49	66 (3.1) 81
Oral mucosal erythema	3 (0.9) 3	2 (0.1) 2
Oral pruritus	134 (38.7) 468	622 (29.1) 841
Stomatitis	31 (9.0) 70	40 (1.9) 47
Vomiting	15 (4.3) 17	18 (0.8) 21
General disorders and administration site conditions		
Chest pain [8]	8 (2.3) 9	10 (0.5) 10
Pyrexia	11 (3.2) 13	21 (1.0) 23
Immune study disorders		
Systemic allergic reaction [9]	7 (2.0) 7	11 (0.5) 12
Infection and infestations		
Upper respiratory tract infection [10]	104 (30.1) 118	424 (19.9). 583
Respiratory, thoracic and mediastinal disorders		
Cough	31 (9.0) 52	78 (3.7) 113
Dyspnoea [11]	16 (4.6) 20	35 (1.6) 51
Nasal congestion	15 (4.3) 22	18 (0.8) 19
Nasal discomfit	11 (3.2) 13	30 (1.4) 31
Oropharyngeal pain	34 (9.8) 52	74 (3.5) 99
Pharyngeal erythema	15 (4.3) 21	7 (0.3) 7
Sneezing	15 (4.3) 27	44 (2.1) 51
Throat irritation	94 (27.2) 314	312 (14.6) 414
Tonsillar hypertrophy	3 (0.9) 7	2 (0.1) 2
Skin and subcutaneous tissue disorders		
Erythema	5 (1.4) 16	5 (0.2) 5
Pruritus	12 (3.5) 19	35 (1.6) 48
Rash [12]	13 (3.8) 15	20 (0.9) 25
Urticaria	12 (0.9) 12	33 (0.1) 37
Vascular disorders		
Flushing	3 (0.9) 3	2 (0.1) 2

N = Number of subjects; % = Percent of subjects, e = Number of events; trials included are: GT-01, GT-02, GT-03, GT-04, GT- 07, GT-08, GT-09, GT-10, GT-11, GT-12, GT-14, GT-16, GT-17, GT-18, GT-19, P05238, P05239.

1: The following preferred terms have been grouped under conjunctivitis: conjunctivitis, conjunctivitis allergic, conjunctivitis allergic 2: The following preferred terms have been grouped under conjunctival hyperaemia: conjunctival hyperaemia, ocular hyperaemia, eye irritation, conjunctival irritation 3: The following terms have been grouped under ear discomfort: ear discomfort, ear pain, ear congestion 4: The following terms have been grouped under abdominal pain: abdominal pain, abdominal pain upper, abdominal pain lower, abdominal pain discomfort, epigastric discomfort, gastrointestinal pain 5: The following terms have been grouped under oral soft tissue conditions: gingival disorders, gingival erythema, gingival oedema, gingival pain, gingival pruritus, gingival swelling, gingival bleeding, gingivitis 6: The following terms have been grouped under lip blister: lip blister, lip disorder, lip ulceration, cheilitis 7: The following terms have been grouped under lip swelling: lip swelling, lip oedema 8: The following terms have been grouped under chest pain: chest pain, non-cardiac chest pain 9: The following terms have been grouped under systemic allergic reaction: anaphylactic reaction, hypersensitivity 10: The following preferred terms have been grouped under upper respiratory tract infection: laryngitis, upper respiratory tract infection, pharyngitis, rhinitis, nasopharyngitis, tonsillitis, sinusitis, post

nasal drip 11: The following preferred terms have been grouped under dyspnoea; dyspnoea, dyspnoea 12: The following terms have been grouped under rash: rash, rash papular, rash pruritic, rash macular, rash generalised, rash erythematous Source: Module 2.7.4 Table 60

8.4. Deaths and other serious adverse events

8.4.1. Deaths

No deaths which were considered to be possibly related to Grazax were reported during any of the trials.

In Study GT-08 (1st year), 1 subject from the placebo group, diagnosed with a subarachnoid haemorrhage (confirmed by CT scan), died during hospitalisation. In Study P05238 a 28 year old male subject died from a multiple drug overdose (hydrocodone, meprobamate, and carisoprodol). The subject had not taken study drugs for approximately 1 month prior to the event.

8.4.2. Other SAEs

8.4.2.1. Pivotal studies

Adults

Study GT-08: During the 5 years of the trial 42 SAEs were reported (in 40 subjects), all assessed as unlikely related to the IMP.

Study GT-14: 2 SAEs were reported in the GT-14 trial; both were considered unlikely related to study drug.

Children

Study GT-12: 5 SAEs in 4 subjects were reported; all were considered unlikely related to study drug.

8.4.2.2. Other studies

No SAEs were reported for the GT-03, GT-04, GT-07, GT-11, GT-16, GT-17, and GT-19 trials.

Adults

Study GT-01: 1 SAE was reported in Period 3, in the treatment group receiving Grazax 25,000 SQ-T. It was not considered related to IMP.

Study GT-02: 7 subjects reported 8 SAEs. Six were considered to be not related to study drug. 1 subject reported an itching feeling of the tongue and a localised oedema of the uvula after intake of the first tablet (25,000 SQ-T) which was considered drug related.

Study GT-10: 8 SAEs in were reported: 3 were considered probably related to IMP (hoarseness and persistent voice problems; unstable severe asthma exacerbations; itching in the mouth, tongue, lips and pharynx with difficulty breathing).

Study P05238: 9 SAEs in 7 subjects were reported; 1 event was assessed as possibly related to IMP (abdominal pain; no abnormality found).

Children

Study GT-09: 1 subject experienced an SAE, reported as an asthmatic crisis (the event appeared 16 hours after tablet intake on day 17) with the following symptoms: dyspnoea, shortness of breath, non-cardiac chest tightness, wheezing and dry cough. The subject had a history of moderate allergic rhinoconjunctivitis and moderate allergic asthma induced by grass pollen. The subject was hospitalised and recovered from the event. Treatment given at the hospital was not reported. The event was judged to be unlikely related to IMP by the investigator but given the temporal relationship the causality assessment was considered as possible.

Study P05239: 5 SAEs in 5 subjects were reported; all were assessed as unlikely related to IMP.

8.4.3. Adverse events with adrenaline use

All AEs that required treatment with adrenaline have been summarised below.

Table 71: Adverse Events with adrenaline use

Treatment	Adverse event	Onset Day	Causality	Severity	Action Taken
GT-02 (Efficacy and safety in adults)					
Grazax	Swollen tongue	73	Probable	Severe	0.2 mg adrenaline SC, 100 mg hydrocortisone IV., 25 mg promethazine IM, discontinued
GT-10 (Compliance and Safety in Adults)					
Grazax	Anaphylactic reaction, asthma	1	Probable	Severe	Beta2-agonist INH, adrenaline 0.3 mg
GT-14 (Efficacy and safety in an adult US population)					
Grazax	Systemic allergic reaction	1	Probable	Moderate	0.2 ml adrenaline SC and 10 mg cetirizine PO discontinued
Grazax	Adverse drug reaction	1	Probable	Moderate	20 mg of loratadine, 0.3 mg adrenaline IM 20 mg prednisone PO; discontinued
Grazax	Systemic allergic reaction	1,2	Probable	Mild	Day 1: 0.3 mg adrenaline SC 20 mg loratadine PO.; Day 2: no treatment, continued in trial
P05238 (Efficacy and safety in an adult US population)					
Grazax	Dysphagia, uvular oedema pharyngeal oedema, and discontinued flush/macular rash on the chest and back, pruritus and chest discomfort	1	Probable	Mild	loratadine, epinephrine (0.3 mg IM.) prednisone
Placebo	Anxiety attack	4	Unrelated	NK	epinephrine (0.3 mg IM.)
P05239 (Efficacy and safety in a paediatric US population)					
Grazax	Pharyngitis, viral	23	NK	NK	epinephrine (0.3 mg IM.)
Grazax	Lip angioedema, slight dysphagia due to the sensation of a lump in the throat, and intermittent cough	1	Probable	Moderate	epinephrine (0.3 mg IM)
Placebo	Wheezing and suprasternal notch chest retraction	137	Unrelated	Moderate	levalbuterol nebulizer, loratadine epinephrine (0.15 mg) prednisone, discontinued

NK = Not known
All events, except for the adrenaline-treated AE reported in the in GT-10 trial, were reported as non-serious.
Source: Module 2.7.4 table 62

8.4.4. Discontinuation due to adverse events

8.4.4.1. Pivotal studies

Adults

Study GT-08

In the 1st year (2005) 16 (5%) subjects treated with Grazax and 8 (3%) subjects treated with placebo withdrew due to 38 AEs. All but 3 events (2 in Grazax group, 1 in placebo) were considered by the investigator as probably or possibly related to the IMP. The AEs leading to withdrawal in the Grazax group were: oedema mouth (4 events), oral pruritus (4), throat irritation (2), pharyngeal oedema (2), bronchospasm, eye pruritus (2), cough, dyspnoea, tongue oedema (2) swollen tongue, fatigue, dysphonia, angioneurotic oedema, malaise, oral pain, oropharyngeal swelling and nausea.

During the 2nd year (2006) 1 subject (< 1%) from the Grazax group and 2 subjects (1%) from the placebo group withdrew due to a total of 5 AEs. The AE leading to withdrawal in the Grazax group considered related to study drug was arthritis.

During the 3rd year (2007) the following AE caused withdrawals from the trial from the Grazax group: moderate asthma, probably related in 1 subject (< 1%).

During the 4th year (2008) and 5th year (2009) of the GT-08 extension trial when no trial drugs were taken, no subjects withdrew due to AEs.

Study GT-14

5 subjects in the placebo group and 10 subjects in the Grazax group withdrew due to AEs. The AEs leading to withdrawal in the Grazax group were: ear congestion, allergic conjunctivitis, diarrhoea, swollen tongue, adverse drug reaction, anaphylactic reaction, labyrinthitis, dyspnoea, oropharyngeal swelling and throat irritation.

Children

Study GT-12: 6 subjects (2%) were withdrawn due to a total of 15 AEs, 2 subjects (2%) in the placebo group and 4 (3%) in the Grazax group. Out of the 4 AE withdrawals observed in the Grazax group, 3 were due to local reactions related to the oral administration of the allergen.

8.4.4.2. Other studies

Table 72: Withdrawals due to AEs in other studies

	N (%) E			Grazax AEs
TRIALS IN ADULTS				
GT-01 Trial – Safety	**Period 1 [c]**	**Period 2 [d]**	**Period 3-4 [e]**	
75,000 SQ-T		1 (8.3%) 1		local oral AEs
Placebo			1 (14.3%) 4	
GT-02 Trial – Efficacy and safety				
Placebo + Loratadine [a] Placebo + Placebo [b]	3 (1.0%) 3			Conjunctivitis (2), viral infection NOS
2,500 SQ-T + Loratadine	4 (2.9%) 4			Sleep disorder NOS, wheezing, herpes simplex ophthalmic, ulcerative colitis
25,000 SQ-T + Loratadine	4 (2.9%) 6			Allergic conjunctivitis, oral pruritus, oropharyngeal swelling, dyspnoea NOS, oedema mouth, headache
75,000 SQ-T + Loratadine 75,000 SQ-T + Placebo	15 (5.1%) 28			Salivary gland enlargement NOS, eye swelling, salivary gland enlargement NOS, swelling face; nausea, tongue disorder NOS, oral pruritus, swelling tongue (2), oedema mouth (4), dyspepsia; urticaria NOS; allergic conjunctivitis, ear pruritus, oral pruritus (2), throat irritation, glossodynia, lip blister,
GT-03 Trial – Safety				
No withdrawals due to AEs				
GT-04 Trial – Safety				
No withdrawals due to AEs				
GT-07 Trial – Safety and efficacy				
Grazax	3 (4.1%) 6			Mouth oedema, cough (2), asthma, oral pruritus, hypersensitivity, itching, feeling warm, chest tightness
GT-10 Trial – Safety and compliance				
Grazax	44 (10%) 83			Most frequent: throat irritation (6), oral pruritus (5) oedema mouth (5), fatigue (4) asthma exacerbations (4)
GT-10 Extension Trial – Safety				
Grazax	7 (3%) 8			gastritis, oral pruritus, chest discomfort and respiratory tract infection, chronic sinusitis, maxillary sinusitis, allergic rhinitis, and eczema.
GT-16 Trial – Immunological parameters and cutaneous reactivity				
Placebo	1 (4%) 4			
Grazax	1 (2%) 1			moderate hypertension
GT-17 Trial – Compliance and safety				
Grazax	12 (5%) 12			oedema tongue (2), epigastralgia, dyspnoea (4) laryngeal oedema, oedema mouth (2) burning mouth syndrome, abdominal pain, upper abdominal pain
GT-18 Trial – Pharmacodynamic effect and tolerability				
Placebo	1 (2%) 1			
Grazax	6 (3%) 8			dyspnoea, pharyngitis, influenza, hypotonia, salmonellosis, paraethesia, oral discomfit, dysphagia
GT-19 Trial – Tolerability of Grazax in combination with antihistamine				
No withdrawals due to AEs				
P05238 Trial – Efficacy and safety in an adult US population				
Placebo	8 (4%) 9			
Grazax	11 (5%) 22			asthma, gingival swelling, chest discomfit (3), lip swelling, dyspnoea, chest discomfit, pharyngeal oedema, headache, dysphagia, dysphonia, palatal pharyngeal erythema, pharyngeal oedema, pruritus, macular rash, oral pharyngeal pain, multiple drug overdose, vertigo

Table 72 (continued): Withdrawals due to AEs in other studies

	N (%) E	Grazax AEs
TRIALS IN CHILDREN		
GT-09 Trial – Safety		
Grazax	2 (9%) 5	
GT-11 Trial – Safety		
No withdrawals due to AEs		
P05239 Trial – Efficacy and safety in a paediatric US population		
Placebo	5 (3%) 15	
Grazax	13 (7%) 31	chest discomfit, dyspepsia (2), throat irritation (3), cough (2), rhinorrhoea, rash (2), rash pruritic, rash generalised, rash erythematous, rash papular, oedema mouth, dyspnoea, non cardiac chest pain, palpitations, abdominal discomfit, dysphagia (2), flushing, hyperhidrosis, dysphonia, hypersensitivity, sensations of foreign body, oral pain, retching, pruritus generalised, ear pruritus

a Active step 1 rescue medication=Loratadine 10 mg; b Placebo step 1 rescue medication; c Single dose exposure, outside the pollen season; d Eight weeks daily dosing, outside the pollen season; e Approximately 15-weeks daily dosing, during the pollen season
N=number of subjects; %=percent of subjects
Source: Module 2.5 Table 12 amended to include details from Table 63 in Module 2.7.4 and text 2.7.4.2.1.4

8.5. Laboratory tests

Clinical laboratory evaluations were not performed in studies GT-01, GT-16, GT-17, GT-18 or GT-19. In all of the remaining studies where laboratory testing was done, no clinically relevant differences in any of the laboratory analyses were observed between treatment groups following treatment with Grazax.

8.5.1. Electrocardiograph and vital signs

No safety concerns in vital signs, physical examination and ECG (where performed) were noted between the active and placebo groups in any of the performed trials.

8.5.2. Lung function

There were no obvious differences over time between the Grazax and placebo groups in any of the lung function measures (where performed) and the lung function seemed not to be affected by exposure to Grazax.

There were no marked differences in the safety profile (including respiratory symptoms) between subjects with asthma and subjects without asthma in any of the trials (including all paediatric trials).

8.6. Post-marketing experience

Grazax was first approved on 14 March 2006 in Sweden. Subsequently, approval was granted for the 32 countries including most of Europe and the USA. The manufacturer (ALK) has withdrawn the marketing authorisation in 8 countries: Bulgaria, Cyprus, Estonia, Hungary, Latvia, Lithuania, Malta and Romania due to commercial reasons.

The cumulative patient exposure from post-marketing to 24-Jun-2015 is estimated to be 211,119 treatment years. The sponsor has submitted 13 PSURs in Europe but only 2 were included in the submission in Australia (covering time frame 25 June 2014 to June 2015).

The sponsor states that overall, the experience gained from post-marketing use of Grazax is in general similar to what has been identified in completed clinical trials and/or what is expected for sublingual immunotherapy. The following adverse drug reactions have been added to the current EU approved SmPC from spontaneous reports post-marketing:

- 19 Jan 2009: Events of 'Palpitations' and 'Hypotension' added based on reports received post marketing
- 25 Jun 2015: Events of 'Eosinophilic oesophagitis' added based on reports received post marketing
- 30 Jul 2015: 'Systemic allergic reactions' changed to 'Anaphylactic reactions' based on a single case of anaphylactic shock reported post marketing.

No safety issues have been identified post-marketing which is considered to impact the overall benefit-risk profile of Grazax.

8.7. Safety issues with the potential for major regulatory impact

8.7.1. Systemic allergic reactions

Systemic allergic reactions are well known in relation to immunotherapy. Systemic allergic reaction may occur in 2 forms; non-life-threatening systemic allergic reaction (also called anaphylactic reactions) and the more severe condition anaphylactic shock. The definition of the 2 types of systemic reactions is different in various publications and guideline documents. Experience with sublingual immunotherapy has suggested a more favourable safety profile compared to subcutaneous immunotherapy. Sublingual immunotherapy is characterised by frequent but mild local reactions (located in the mouth and throat), and rare systemic reactions.

Delayed systemic reactions (most frequently urticaria and mild asthma and/or rhinoconjunctivitis) that may develop after several hours or within the first day or 2 have also been reported during the use of sublingual immunotherapy, but they are not common and some of these delayed reactions may be symptoms of a subject's underlying allergic disorder.

In the clinical trials with Grazax, systemic allergic reactions as such were not reported; however some symptoms consistent with systemic reactions were reported.

One case of urticaria led to withdrawal in Study GT-02 and would usually be considered a significant systemic reaction. However, the number of subjects reporting urticaria during the trial was similar between treatment groups including placebo. The same pattern was observed in Study GT-08 (1st year), where similar numbers of subjects (approximately 1%) with urticaria were observed between treatment groups. None of the events led to withdrawal. In Study GT-10 approximately 1% of subjects reported urticaria. Only 1 of these events (mild localised urticaria in mouth) led to withdrawal.

During the GT-14 trial in the US, 3 non-serious significant AEs occurred (all in the Grazax group, all assessed as related to treatment) which were treated with adrenaline although none of the events included signs of hypotension. All subjects recovered from the events.

One subject experienced a moderate (investigator's assessment) systemic allergic reaction about 5 minutes after first intake (swelling of lips, itchy mouth, tongue and throat and dysphagia, but no abnormalities in the oral examination). Ten minutes after first symptom onset the subject was treated with 0.2 ml adrenaline SC and 10 mg cetirizine PO.

One subject experienced itchy throat, itchy mouth, dry cough and one hive on left side of lower lip immediately after first intake. Furthermore, uvula was reported as being red. 20 mg of loratadine and 0.3 mg adrenaline IM was administered.

One subject experienced a systemic allergic reaction 6 minutes after first intake, described as mild by investigator. Symptoms included itching under the tongue, throat, ears and nose, sneezing, rhinorrhoea, throat irritation. The subject was treated with 0.3 mg adrenaline SC and 20 mg loratadine PO. The next day the subject experienced another episode of anaphylactic reaction. No treatment was instigated due to the second event and the subject continued in the trial.

During Study P05238 2 subjects were treated with 0.3 mg adrenaline. One of the administrations was due to an adverse reaction to IMP (dysphagia, uvular oedema and pharyngeal oedema) that occurred following the first administration of the tablet under the care of the investigator (Grazax group). The event was categorised as mild in severity by the investigator. The other administration was given inappropriately for an anxiety event unrelated to IMP (placebo group).

During Study P05239, 3 subjects received adrenaline at Day 1, Day 23, and Day 137. On Day 1 the administrations was given in response to an adverse reaction to the IMP (Grazax group). The subject developed lip angioedema, slight dysphagia due to the sensation of a lump in the throat, and intermittent cough within minutes following the first IMP administration. The symptoms resolved within minutes after adrenaline administration (0.3 mg IM). The investigator graded this event as moderate in severity. The other administration (0.3 mg IM) was received for viral pharyngitis in an emergency department on Day 23, where adrenaline administration was not indicated (or medically appropriate) (Grazax group). The third adrenaline administration (0.15 mg IM) on Day 137 was in response to wheezing and suprasternal notch chest retraction (placebo group). The investigator graded the event as moderate in severity and unrelated to IMP.

Eight of 43 subjects (19%) in Study GT-04 reported a total of 16 treatment related AEs that could indicate changes in asthma symptoms and in Study GT-07, 26 of 114 subjects (23%) reported a total of 36 AEs related to asthma. All subjects included in the 2 trials suffered from mild to moderate grass pollen induced asthma and there were no obvious differences between treatment groups in numbers or frequency of AEs and no indications of asthma aggravation in actively treated subjects compared to placebo.

8.8. Safety related to drug-drug interactions and other interactions

Drug interactions were not studied. No drugs have been contraindicated in the proposed PI due to drug interaction.

8.9. Evaluator's overall conclusions on clinical safety

The total number of subjects exposed to Grazax in the clinical development program was 2,482. Overall, 72% of subjects receiving Grazax reported treatment related AEs. These AEs were primarily reported during the first 3 months of treatment (56% reported AEs within the first 3 months of treatment).

Oral pruritus was the most frequently reported related AE, experienced by 30% of the subjects treated with Grazax. Throat irritation, mouth oedema and ear pruritus were also frequently reported (by 8 to 16% of the subjects treated with Grazax). These side effects may be sufficiently bothersome to lead to discontinuation of therapy.

In Study GT-19 which used antihistamines in addition to Grazax there was no statistically significant difference in the number of subjects reporting local allergic reactions when treated with antihistamine or placebo antihistamine.

Systemic allergic reactions were uncommon but did occur during the studies. No anaphylactic shock was reported in any of the clinical studies but has been reported as a spontaneous post marketing event.

9. First round benefit-risk assessment

9.1. First round assessment of benefits

The benefits of Grazax in the proposed usage are:

- Effectiveness in relieving symptoms of rhinoconjunctivitis symptoms and to lesser extent use of rescue medication was shown in 2 studies in adults and 2 studies in children with clinically relevant symptoms and diagnosed with a positive skin prick test and specific IgE test to Timothy grass pollen.
- In most of the studies where immunological endpoints were included, the immunological changes of Grazax immunotherapy have been consistent and statistically significant although the exact clinical significance of the findings remains to be elucidated.

9.2. First round assessment of risks

The risks of Grazax in the proposed usage are:

- Anaphylactic reactions including anaphylactic shock have been observed with Grazax during post-marketing surveillance. The risk of systemic allergic reactions with Grazax is small and most likely to occur at the first does and may be manageable with appropriate supervision of the initial doing.
- Local allergic reactions of varying severity are common particularly oral pruritus, throat irritation, mouth oedema and ear pruritus.
- Acute asthma may occur.
- Use in children below 5 years of age and in elderly above 65 years of age as well as use in pregnant and lactating women was excluded from the trials and so is unknown. Use in children < 5 is not requested and is unlikely but efficacy and safety in the elderly is unknown.

9.3. First round assessment of benefit-risk balance

The benefit-risk balance of Grazax, given the proposed usage, is favourable.

10. First round recommendation regarding authorisation

Based on the clinical data submitted it is recommended that Grazax be approved for the following indication:

> *Grazax is indicated for treatment of Timothy grass (Phleum pretense) pollen allergic rhinitis with our without conjunctivitis in adults, adolescents and children (above the age of 5) with clinically relevant symptoms, confirmed by a positive cutaneous test and/or a positive titre of the specific IgE to Phleum pratense.*

11. Clinical questions

No clinical questions were raised in this evaluation.

12. Second round evaluation of clinical data submitted in response to questions

No new clinical information was provided.

13. Second round benefit-risk assessment

No new clinical information was submitted in response to questions. Accordingly, the benefit and risks of Grazax are unchanged from those identified in the first round evaluation.

14. Second round recommendation regarding authorisation

The recommendation regarding authorisation is unchanged from the first round evaluation.

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