Integrated Clinical Trial Report

Observational national clinical trial of safety and tolerance in patients suffering of an allergic grass pollen rhinitis and treated by GRAZAX® in real life settings

Investigational Medicinal Product: Grazax® tablet (75,000 SQ-T) oral lyophilizate

Clinical trial ID:	GT – 15
EudraCT No.	2007 – 003772 – 20
Indication:	Treatment of grass pollen-induced allergic rhinoconjunctivitis in adult patients presenting with clinically relevant symptoms diagnosed with a positive skin prick test and/or a specific IgE test to grass pollen
Development Phase:	IV
First subject first visit:	November 2007
Last subject last visit:	December 2008
Investigator:	Dr. [redacted]
Trial centre:	[redacted] R
Sponsor:	Laboratoire ALK-ABELLO (previously Laboratoire ALLERBIO) 7 Place de la Défense 92400 COURBEVOIE - FRANCE
Clinical Trial Manager:	[redacted] MD, ALK-Abelló France
Report No. and date:	Trial GT - 15, 2009, 23-September-2009

This trial was conducted in compliance with the principles of *ICH Good Clinical Practice*.

Synopsis – Trial GT - 15

Title of Trial Observational national clinical trial of safety and tolerance in patients suffering of an allergic grass pollen rhinitis and treated by GRAZAX® in real life settings. EudraCT 2007 – 003772 – 20
Investigator Dr. [redacted]
Trial Centre 130 allergologists or pulmonologists
Publication None
Trial Period First subject first visit – November 2007 Last subject last visit – December 2008
Objectives Primary: To evaluate the safety profile of GRAZAX® given to patients with grass pollen-induced rhinitis and conjunctivitis. Secondary: • To describe the patient's integrated care pathway • To evaluate overall satisfaction of patients receiving GRAZAX® • To describe the impact of GRAZAX® on quality of life and occupational activities (RQLQ) To describe treatment compliance with GRAZAX® during the first 4 weeks of treatment
Methodology A multi-centre, open-label, interventional, randomized, observational study.
Number of Subjects Planned and Analysed 600 planned 629 randomised 628 treated 523 completed 106 withdrawn – Reason: • Withdrawal of consent before treatment 1 (0.9%) • Poor compliance 5 (4.7%) • Adverse event 70 (66.0%) • Patient lost to follow-up 15 (14.2%) • Lack of efficacy of treatment 4 (3.8%) • Other reason 11 (10.4%) 628 analysed

Diagnosis and Main Inclusion Criteria

Adult subjects (male or female), over 18 years of age, presenting with grass pollen allergic rhinitis previously diagnosed (previously performed prick-test and/or specific IgE assay available) and for which treatment with tablet-based SIT (Specific Immunotherapy) is initiated:

- Who were informed and gave oral and written consent to participate in the study
- For whom GRAZAX® was prescribed in agreement with the SPC
- Not simultaneously participating in another clinical study

In women of child-bearing potential, an effective method of contraception must be used throughout the whole duration of the study.

Investigational Medicinal Product, Dose and Mode of Administration, Batch Number(s)

Grazax®

Orodispersible tablet (Oral lyophilizate)(75 000 SQ-T)

Oral

1 intake of 1 tablet daily

batch No. ??

Reference Therapy, Dose and Mode of Administration, Batch Number(s)

Not applicable

Duration of Treatment

10 months at maximum

Criteria for Evaluation – Safety

- Safety profile (AE and SAE)
- RQLQ quality of life mini-questionnaire by E.F. JUNIPER
- Patient overall satisfaction evaluated by questionnaire and visual analogue scale (VAS)
- Physician's overall satisfaction evaluated by questionnaire
- Simple pharmacoeconomic data (medical visits, sick leave from work, etc.)
- Data on the patient's integrated care pathway and diagnosis of certainty of allergic rhinoconjunctivitis.

Statistical Methods

- For quantitative parameters: mean, standard deviation, minimum, maximum and missing data, and possibly median and quartiles.
- For qualitative parameters: incidence, percentages per modality analyzed.

Some criteria have been cross-checked with each other, using two-sided tests at a α risk of 5%.

Qualitative variables have been compared using a chi^2 test (or Fisher's exact test, according to sample size), quantitative variables using the Student's t test (or Wilcoxon's test, according to distribution).

Multiple pollen sensitization (Yes / No), allergic asthma (Yes / No) and previous SIT (Naïve / switch / Immediate switch) sub groups were compared in terms of the presence of at least one AE using univariate logistic regression analysis. The Odds Ratio for each sub group has been estimated.

The course and outcome of VAS scores throughout the 8 weeks was analyzed using repeated measures ANOVAs with the week, the pollen count, polysensitization, allergic asthma at enrollment and previous SIT as fixed effects.

Safety Results

628 patients were treated with GRAZAX® for 5.5 months on average with a single intake, starting on day one.
338 (45.7%) of them experienced 750 adverse events.
Oral pruritus was the most commonly reported event, 106 patients (16.9%); followed by oral paresthesia and sensation of oral edema which affected 48 (7.6%) and 40 (6.4%) patients respectively. The majority of AEs were of mild or moderate severity.

The presence of polysensitization, asthma, duration and severity of rhinitis did not affect the risk of occurrence of adverse events while this risk depends on previous specific immunotherapy (SIT): patients who had received previous SIT discontinued between one month and 2 years prior to initiating GRAZAX®, were at significantly less risk for AEs than patients never treated with SIT (p=0.01).

After administration of the first intake of GRAZAX®, 43.2% of patients did not experience any reaction. Among patients who experienced a reaction, this reaction was considered as not clinically significant in 96% of patients, i.e., these reactions were less than 30 minutes in duration and did not require any prescription of symptomatic therapy.
The risk of presenting with an AE throughout the whole duration of treatment with GRAZAX® was dependent on the reactions experienced at time of first dosing. Indeed, the risk of an AE was markedly lower in patients who did not present with an adverse reaction at the time of first dosing.

Seventy patients were withdrawn from the study for adverse events and three of them presented with a serious adverse event (oral ulceration, episode of ulcerative colitis, asthma attack and malaise).

Other results

- Scores for severity of functional impairment as measured on a VAS changed according to the week of the grass pollen season and grass pollen counts.
- In patients, rhinitis-related impairment was mild or moderate and thus the impact of GRAZAX® on quality of life and occupational activities was low.
- 85% of patients and 86% of investigators were satisfied or very satisfied with GRAZAX®.
- 77% of patients planned to continue treatment with GRAZAX®.
- 94% of patients considered that the intake of a tablet of GRAZAX® was easy or very easy.

Conclusions

GRAZAX® was well-tolerated: although common, the adverse events were mainly local, minor and well-tolerated reactions.
The good safety profile of Grazax® starting with the first intake demonstrated that intake titration at the start of treatment was not necessary.

Date of the Report

23 September 2009

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