Addendum n° 2 to 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 GRAAL extension third year

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

Clinical trial ID:	GT-15 – Study GRAAL 3rd Year Extension (2010), France
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 3rd year:	11 January 2010
Last subject last visit 3rd year:	11 October 2010
Investigator:	Dr. [redacted]
Trial centre:	[redacted] [redacted] France
Sponsor:	Laboratoire ALK-ABELLO 7 Place de la Défense 92400 COURBEVOIE - FRANCE
Clinical Trial Manager:	[redacted], MD, ALK-Abelló France
Report No. and date:	Final version, 26 September 2011

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

Synopsis – Trial GT-15 – Extension 3rd year

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: GRAAL extension third year. EudraCT 2007-003772-20
Investigator Dr. [redacted] France
Trial Centres 95 allergists or pulmonologists in France
Publications None
Trial Period for Third Year *First subject first visit* – 11 January 2010 *Last subject last visit* – 11 October 2010
Objectives Primary: To evaluate the safety profile of a third year of use of GRAZAX® given to patients with grass pollen-induced rhinitis and conjunctivitis. Secondary: • To describe treatment compliance with GRAZAX® during the third year of use • To evaluate overall satisfaction of patients receiving GRAZAX®
Methodology for the Third Year A multi-centre, open-label, interventional, observational extension study.
Number of Subjects Planned and Analysed for the Third Year 350 maximum planned (who accepted at the end of the second year to follow a third year) 277 enrolled 277 treated 272 completed 5 withdrawn early: 1 adverse event, 2 poor compliance, 2 treatment inefficacy 277 analysed
Diagnosis and Main Inclusion Criteria for the Third Year Patients who accepted at the end of the second year to follow a third year of treatment and • Who participated in the entire first and second years of the study • Who were compliant to the treatment during the first and second years • Who were informed about the study and gave oral and written consent to participate in the third-year extension • For whom GRAZAX® was prescribed in agreement with the SPC • Who were not simultaneously participating in another clinical study • In women of child-bearing potential, an effective method of contraception had to be used throughout the duration of the third-year extension.
Investigational Medicinal Product, Dose and Mode of Administration, Batch Number(s) No modification except for the batch number for the third year treatment: #126555 (expiry date: 11/2012)
Reference Therapy, Dose and Mode of Administration, Batch Number(s) Not applicable.
Duration of Treatment for the Third Year A maximum of 8 months.

Safety Criteria for the Third Year Evaluation

- Safety profile (AE and SAE)
- Patient overall satisfaction evaluated by questionnaire
- Physician overall satisfaction evaluated by questionnaire

Statistical Methods

The Full-Analysis Set (FAS / Intention To Treat [ITT]) – all treated subjects was used. The Safety population was defined as all enrolled patients who took at least one GRAZAX® tablet.

For quantitative parameters: mean, standard deviation, minimum, maximum and missing data, and in some cases median and quartiles.

For qualitative parameters: incidence, percentages per modality.

Some criteria were cross-checked using two-sided tests at a α risk of 5%.

Qualitative variables were compared using a chi² 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) 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 was estimated.

Demography of Trial Population in Third Year

Mean age of the population was 38.6 ± 10.4 years, with a balanced sex ratio (male 53.8%; female 46.2%). The majority (97.1%) continued the SLIT on a seasonal basis. At the start of study extension, 97.4% of patients had a normal physical examination, and 93 patients (33.6%) had an immediate reaction (*ie* within 30 minutes, no symptomatic treatment) to first intake.

Eighty-eight patients (31.8%) were asthmatic, 188 (67.9%) were polysensitised, and 8 (2.9%) received per-annual SLIT.

Results

Third Year Safety

A mean 5.5 ± 1.2 months of treatment was administered in this third year of the study. Out of the population of 277 patients who received a third-year of treatment, 13 patients (4.7%) presented with 21 adverse events (AEs). No individual AE occurred in more than two patients (0.7%). The following events were reported in two patients each; nausea, asthenia, oral pruritus, pharyngitis and tonsillitis. All other events were reported in one patient only. No severe events were reported, 13 events (7 patients) were moderate and 8 events (6 patients) were mild. AEs were considered related to Grazax® intake in 5 patients (1.8%).

Immediate reactions to the first intake at reintroduction of GRAZAX® (within 30 minutes and not requiring symptomatic treatment; not considered AEs) were reported in 33.6% of patients, all of which were tolerable.

The occurrence of an immediate reaction to the first intake increased the risk of having any AE or a related AE at any time during the study, compared to patients who did not have an immediate reaction (p=0.012 and p=0.045 respectively).

The patient's asthmatic and polysensitisation status did not significantly affect the risk of having an AE.

No serious adverse events occurred and one patient discontinued the treatment due to related AEs, all of which were loco-regional reactions to study treatment.

Safety Comparison Over Three Treatment Years

A significant reduction in the incidence of AEs occurred with each consecutive treatment year. When comparing the annual incidence of AEs during the 1st, 2nd and 3rd years in the 277 patients treated for 3 years, the rate of patients presenting an AE decreased significantly from 43.7% to 14.8% in the second year and to 4.7% in the third year ($p<0.001$). The same held for related AEs (from 38.6% to 11.2% to 1.8% respectively), for loco-regional AEs (from 33.2% to 11.2% to 1.8%, respectively), and for AEs occurring between the first and second administrations (from 20.9% to 8.3% to 0.7%)($p<0.001$ for all).

The incidence of moderate to severe locoregional AEs decreased with each successive year, being 18.3% for GRAAL 1 (628 patients), 4.9% for GRAAL 2 (367 patients) and 1.1% for GRAAL 3 (277 patients).

A similar pattern of cumulative incidence of the first AE was apparent in all three treatment years (N=277).

Timing of the occurrence of pertinent AEs (oral and ear pruritus, oral paraesthesia, mouth oedema, and throat irritation) was also similar in all three treatment years with the majority of pertinent AEs reported during the first week following first treatment intake, although this extended to the first month of treatment during the initial year.

Neither the asthmatic or polysensitisation status impacted on the likelihood of AEs occurring in any of the treatment years.

Similarly, a reduction in the incidence of immediate reactions to first seasonal intake (*ie* not considered to be AEs) was seen with each consecutive treatment year and a comparison of annual incidences of immediate reactions showed a significant reduction in incidence in the 2nd and 3rd years relative to the initial year reaching a plateau by the third year (GRAAL 1, 56.3%, GRAAL 2, 39.4%, GRAAL 3, 33.6%; $p<0.0001$).

The rate of patients with an immediate reaction who subsequently had AEs during treatment decreased with successive years (56.6% to 27.5% to 4.3%).

The populations completing all three years had significantly less polysensitivity, received more SLIT and more were positive for IgE when compared to the population receiving one or two years of treatment.

Investigator and Patient Satisfaction

The rate of compliance during this third year of treatment was 90.3%, with non-compliance mostly due to omissions (*ie* not intolerance).

Overall, 94.9% of patients and 95.9% of investigators were satisfied or very satisfied with the third year of GRAZAX® treatment.

The rate of satisfaction in 84 of the 90 patients who chose not to continue with a third treatment year was 79.8% (missing data for 6 patients).

Conclusions

This third year of the GRAAL GT-15 study showed an excellent safety profile in the 277 patients treated with Grazax® in an outpatient setting in France and according to the MA requirements, during a third consecutive pollen season.

Compliance in the third year was very high and treatment was well tolerated. With each consecutive year of treatment, significant reductions in the incidence of adverse events were seen relative to both the initial year and second year extension. Analysis of the treatment over three consecutive years suggests that patients have an increased tolerance threshold with each consecutive treatment year.

Although the incidence of immediate reactions following first administration reduced significantly with consecutive treatment years, one-third of patients still reported an immediate reaction at reintroduction in the third year. This highlights the importance of maintaining the first annual seasonal administration of GRAZAX® in the presence of the patient's physician with a 30-minute surveillance period.

These results confirm the value of continuing daily GRAZAX® treatment for a third year in a pre- or co-seasonal schedule, as well as per-annual.

Date of the Report

26 September 2011

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