Addendum n° 1 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 second year

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

Clinical trial ID:	GT-15 – Study GRAAL Extension 2nd year- 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 2nd year:	09 January 2009
Last subject last visit 2nd year:	22 October 2009
Investigator:	Dr. [redacted]
Trial centre:	[redacted] [redacted] Fr
Sponsor:	Laboratoire ALK-ABELLO 7 Place de la Défense 92400 COURBEVOIE - FRANCE
Clinical Trial Manager:	[redacted] MD, ALK-Abelló France
Report No. and date:	Trial GT-15 – GRAAL extension 2nd year, 2009, 29-November-2010

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

Synopsis – Trial GT-15 – Extension 2nd 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 second year. EudraCT 2007 – 003772 – 20
Investigator Dr. [redacted] Nantes
Trial Centres 112 allergists or pulmonologists in France
Publications None
Trial Period for 2nd year *First subject first visit* – 09 January 2009 *Last subject last visit* – 22 October 2009
Objectives Primary: To evaluate the safety profile of a second year use of GRAZAX® given to patients with grass pollen-induced rhinitis and conjunctivitis. Secondary: • To describe treatment compliance with GRAZAX® during the second year of use • To evaluate overall satisfaction of patients receiving GRAZAX®
Methodology for second year A multi-centre, open-label, interventional, observational extension study.
Number of Subjects Planned and Analysed for second year 400 maximum planned (who accepted at the end of the first year to follow a second year) 371 enrolled 367 treated 351 completed 16 withdrawn – 7 for adverse event; 2 lost to follow-up; 7 for other reasons 367 analysed
Diagnosis and Main Inclusion Criteria for extension The patients who accepted at the end of the first year to follow a second year and • Who participated to the whole 1st year of Graal study • Who were compliant to the treatment during this first year • Who were informed and gave oral and written consent to participate in the extension 2nd year • 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 extension 2nd year.
Investigational Medicinal Product, Dose and Mode of Administration, Batch Number(s) No modification excepted the Batch Number for the second year: 684332 (expiration : 01/2010)
Reference Therapy, Dose and Mode of Administration, Batch Number(s) Not applicable
Duration of Treatment for the extension 2nd year A maximum of 8 months

Criteria for Extension 2nd year Evaluation– Safety

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

Statistical Methods

The following analysis sets were used:

Full-Analysis Set (FAS / Intention To Treat (ITT)) – all treated subjects

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 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 has been estimated.

Demography of trial population

Mean age of the population was 37.2 years, with a balanced sex ratio (male 53.4%; female 46.6%). The majority (95.4%) continued the SLIT on a seasonal basis. At time of entry in the study, the physical examination was normal in 99.1% of cases.

Extension 2nd year
Safety Results

Out of the total population, 65 patients (17.7%) presented with 111 adverse events. The most common events were, in accordance with previous studies, oral pruritus (23 patients; 6.3%) and oral paraesthesia (8 patients; 2.2%), of mild or moderate intensity. The other events were of a broad variety and affected less than 1% of the subjects. Adverse events were considered as related to intake of Grazax® in 53 patients (14.4%).

The asthmatic status of the patients slightly increased the risk of having an adverse event but not the type of event, as compared to non-asthmatic patients, whereas polysensitisation had no influence on the incidence of AEs.

The occurrence of an immediate reaction to the first intake at reintroduction of Grazax® (142 patients;38.7%) did increase the risk of having an adverse event but not the type of event, as compared to the patients who did not have an immediate reaction.

When comparing the incidence of adverse events occurring during the 1st and the 2nd year of GT-15, the number of patients presenting an AE decreased significantly from 46.9% to 17.7% ($p < 0.001$). The same conclusions hold for related AEs (from 39.5% to 14.4%), for loco-regional AEs (from 36.5% to 12.5%), and for AEs in patients with an immediate reaction (from 21.0% to 7.6%).

One patient died from cardiac arrest, not related to study treatment and another experienced a malaise leading to emergency care for 1 day, not related to treatment. Six patients discontinued the treatment for an adverse event, all were loco-regional reactions to study treatment.

Other results (secondary objectives)

- 91.4% of patients and 91.3% of investigators were satisfied or very satisfied with GRAZAX®.
- 88.3% of patients planned to continue treatment with GRAZAX®.

Conclusions

This second year of the Graal study conducted on a population of over 350 patients treated with Grazax® in outpatient practice according to the MA requirements and in the same country, provided safety information which confirmed the safety profile demonstrated in phases I, II and III of clinical development. It confirms the interest of continuing with ITS treatment for a second year.

It also underlines the importance of a first reintroduction of GRAZAX® at the physician office, to detect new possible adverse events and to inform the patient about them.

Date of the Report

29 November 2010

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