2 SYNOPSIS

Title of Trial: A multicentre randomised placebo-controlled, double-blind clinical trial for evaluation of safety and efficacy of preseasonal specific immunotherapy with a hypoallergenic extract of a 6 grass and *rye* (Grasses plus *Rye*) pollen mixture in patients with rhinoconjunctivitis +/- asthma bronchiale	
Investigator(s): [redacted]	
Trial Center(s): 4 sites (one at Porto, two at Lisboa and one at Setúbal)	
Publication (reference): NA	
Trial Period (years): **Start of Treatment:** Oct/November 2007 onwards **Planned End of Treatment:** February 2009 (blind) February 2010 (open third year phase) **Planned End of Study:** October 2010 **Open Label Period:** 10/2009-02/2010 if efficacy of active treatment has been demonstrated	**Phase of Development:** IV
Objectives: To prove the hypothesis that the allergoid preparation of an extract of a 6 grasses plus *rye* pollen mixture is suitable for an efficacious treatment of grass pollen allergic patients with SIT and that the trial preparation is sufficient to suppress allergic symptoms caused by natural grass pollen exposure – **The number of patients with an improvement of the threshold concentration after 2 years of treatment.**	
Methodology: This clinical trial will be performed as a randomised, double-blind, placebo-controlled phase IV study in two parallel groups.	
Number of Subjects: The study drug will be tested versus placebo in 75 patients randomised.	
Diagnosis and Main Criteria for Inclusion: - Patients suffering from IgE-mediated, moderate to severe seasonal allergic rhinitis with or without controlled bronchial asthma (PEF and/or FEV_1 at	

least 80% predicted normal), attributable to grass/*Secale* pollen ***and***

- In the course of the year: major allergy symptoms during grass/*Secale* pollen season ***and***
- Symptoms of allergic rhinoconjunctivitis against grass/*Secale* pollen allergens requiring medication during the last grass pollen season ***and***
- Proven clinical relevance of grass pollen allergy by positive conjunctival provocation test result using a natural grass pollen extract ***and***
- Positive Prick Test reaction to grass pollen allergens demonstrated by allergen wheal diameter > 3mm (to be demonstrated in a valid skin prick test: negative NaCl control wheal < 3mm, positive Histamine (0.1% control wheal ≥ 3mm) ***and***
- Positive EAST to grass pollen ≥ 1.5 kU/L to be determined in central laboratory
- For female patients: effective contraception and negative pregnancy test result. Highly effective methods of birth control are defined as those which result in a low failure rate (i.e. less than 1% per year) when used constistently and correctly such as implants, injectibles, combined oral contraceptives, some IUDs, sexual abstinence or vasectomised partner. No pharmacological interactions are known for hormonal contraceptives and specific immunotherapeutic preparations.
- Written informed consent

Test Product(s): Dose and Mode of Administration, Batch Number(s):
Depot allergoid from 6 grass plus *rye* pollen allergens or placebo

Sterile suspension for subcutaneous injection

Subcutaneous injection in the upper arm

Strength A ([redacted]), Strength B ([redacted])

The maintenance dose is equivalent to [redacted] grasses group 5 major allergen

Duration of Treatment: Pre-seasonal with a minimum of 7 injections, up to 5 months prior to grass pollen season

Injection Intervals: 7 days (+7 days)

Reference Therapy(ies), Dose and Mode of Administration, Batch Number(s): Not applicable

Criteria for Evaluation:

Efficacy: The efficacy of the allergoid preparation to grass pollen allergic patients will be evaluated based on the following:

- Conjunctival Provocation Test (CPT)
- Assessment of rhinoconjunctivitis at the end of the grass pollen season according to a Visual Rating Scale
- Immunologic changes: specific IgG_4, IgG_1

Pharmacokinetics:

Not applicable

Pharmacodynamics:

Not applicable

Safety: Tolerability and Safety of treatments during the entire study period

Statistical Methods:

A detailed Statistical Analysis Plan (SAP) had be developed for the study.

Due to premature termination of clinical trial only global and general items will be described. Quantitative variables were compared between groups, as appropriate. Qualitative variables were described as propotions.
The threshold dose of the patients´ reactivity to the specific conjunctival provocation test to grass and *rye* allergens will be determined before and after 1, 2 and 3 treatment courses after the grass pollen season in October.
At the end of each grass pollen season during treatment the patients will assess their allergy severity on a Visual Rating Scale.
Blood samples will be taken at entry to determine allergy specific serum IgG_1 and IgG_4 and at further timepoints during the course of treatment.
At each visit the patients will be asked by the investigator for any changes in her/his state of health and all Adverse Events will be documented.

Summary and Conclusions:

Subject Disposition: A total of 31 patients participated in the study out of the

necessary 75 patients expected.

Demographics and Baseline Characteristics: In total of 31 patients (14 male and 17 female) with mean aged 33,16 years enrolled in the study.

Efficacy Results: Does not exist, due to premature termination of clinical trial.

Pharmacokinetic Results:

Not applicable

Pharmacodynamic Results:

Not applicable

Safety Results: Does not exist, due to premature termination of clinical trial. The patients who received study drug tolerated with no serius adverse events.

Conclusions:

The run-in period was delayed so no ethical reasons to mantain the study. The study was premature terminated.

Date of Report / Version No.: 17-06-2011