Sponsor Protocol Code	ParLais/09
EUDRACT Number	2008-007657-12
Name of the Sponsor	Lofarma S.p.A.
Sponsor Organization Address	Viale Cassala, 40 20143 Milano Italia
Coordinating Investigator, study Centre	Clinica Malattie Apparato Respiratorio e Allergologia Università di Genova, Italy. Eight investigational sites participated in the study. The sites were located in the regions: Liguria, Piemonte, Sardinia.
Date First Subject Entered	28 December 2009
Date Last Subject Completed	16 September 2010
Study phase:	III
Studied period (years):	About 9 months
CRO	CROnos Ricerche Cliniche s.r.l
Name of Sperimental product:	Lais Parietaria sublingual tablet.
Name of active ingredients:	Sublingual immunotherapy is prepared in oromucosal tablets (to be taken sublingually) containing Parietaria (Parietaria judaica 50%, Parietaria officinalis 50%). Excipients: lactose 110 mg; microcrystalline cellulose 37 mg; silicon dioxide 1 mg; magnesium stearate 2 mg per tablet). The placebo had the same composition except for the absence of the allergenic extract.
Route of administration and dose:	The therapeutic scheme does not include any induction phase, but only the maintenance one. In the maintenance phase for all three treatment arms and for the entire duration of treatment, the dosage of one tablet of 1000 AU (Allergenic Units) per day was taken, preferably in the morning, on an empty stomach, and placed in the oral cavity and hold until complete dissolution (1 or 2 minutes). The duration of the pre-coseasonal SLIT scheme was 25 weeks (as for the placebo), of which 8 are pre-seasonal and 17 are co-seasonal. The duration of the co-seasonal SLIT scheme was instead of only 17 weeks, preceded by 8 weeks of placebo to ensure the maintenance of the double blind.
Title of study:	Evaluation of the efficacy, safety, tolerability of use and treatment adherence in two different dosing schedules, pre-coseasonal and coseasonal, of a sublingual allergoid (Lais Parietaria) administered to patients suffering from oculorinitis with or without Parietaria bronchial asthma. Randomized, double-blind, multicenter, parallel-group, placebo-controlled study.
Objective:	To evaluate the clinical efficacy, safety and tolerability of use and therapeutic adherence of specific sublingual immunotherapy (SLIT), of two different dosage regimens without any updosing.
Endpoints:	The primary objective of the study is to compare the therapeutic efficacy of two different dosage regimens, pre-co-seasonal and co-seasonal, of Lais Parietaria sublingual, versus placebo. The primary endpoint assessment parameter will be the change in standardized area under the curve (AUC) obtained from the combined symptom and symptomatic drug consumption score (SMS = Symptom-Medication-Score) recorded from the beginning to the end of the pollen season. and reported daily in patient clinical diaries.

	The secondary objectives of the study are as follows: - Reduction of symptoms and the consumption of symptomatic drugs, evaluated separately - Days without symptoms, days without the use of symptomatic drugs - Evaluation of the patient's QoL. - Safety (incidence of Adverse Events) During the study it was allowed to use concomitant anti-allergic therapy, as needed, consisting of the following symptomatic drugs: - Oral antihistamines (levocetirizine 5 mg tablet or desloratadine 10 mg tablet) in case of mild or moderate symptoms; - Salbutamol (1-2 puffs as needed), in case of mild and moderate symptoms of the lower respiratory tract; - Ocular antihistamines (levocabastine drops) in case of conjunctivitis; - Inhaled and / or bronchial steroids, as needed; - Short courses of oral prednisone (25 mg tablet) in case of severe symptoms and in the opinion of the doctor. Clinical diary. The combined evaluation of the symptomatic score / symptomatic drug intake as needed was carried out by filling in a specific clinical diary daily during the pollen season. Clinical symptoms to be recorded were: nasal itching, sneezing, rhinorrhea, obstruction, ocular itching, lacrimation, wheezing, difficulty breathing, nocturnal awakenings, chest tightness. Each of these symptoms were assigned a score of 0 (absent), 1 (mild), 2 (moderate), 3 (severe). The maximum daily score was therefore 30. The patient also had to report in the diary the consumption of permitted antiallergic drugs (systemic antihistamine, ocular antihistamine, short acting bronchodilator, nasal, bronchial or systemic inhaled steroids). The QoL was evaluated by means of a specific questionnaire ("Rhinasthma") to be administered to the subjects during the peak of the pollen season (V2) and at the end of the study (V3). The Rhinasthma questionnaire consists of 30 questions regarding the impact of rhinitis and asthma on everyday life. From the responses, 4 factors are derived regarding the upper and lower airways, their sum and the overall impact. On the occasion of each visit scheduled by the study, the Investigator recorded on the CRF the possible occurrence of side effects or unwanted events, spontaneously reported, reported on request or clinically observed, together with their intensity and duration. All patients including those who concluded the study and patients who discontinued therapy both for reasons related to the study treatment and for reasons independent of the study treatment, who have taken even a single dose of "drug" were evaluated for tolerability. Tolerability will be assessed by considering all the observed side effects whose link with the treatment is possible, probable or certain.
Population of trial subjects	Main inclusion criteria. Patients will need to meet all of the following inclusion criteria: 1. Age between 18 and 60, of both sexes. 2. Clinical history of mild intermittent to moderate / severe persistent rhinitis (oculorinitis) with or without intermittent allergic asthma for at least 2 years.

	3. Presence of symptoms only during the Parietaria pollen season. 4. Parietaria sensitization confirmed by positive skin prick test for Parietaria with wheal having an average diameter of 3 mm greater than the negative control wheal. 5. Patients with a sufficient degree of cooperation and understanding who have consented to the study and provided the signed informed consent for confirmation.
Study Design	Phase III, double-blind, multicenter, prospective, randomized, parallel-group, placebo-controlled study. The study includes, in addition to the enrollment visit and start of therapy (V0), other 3 mandatory visits (V1, V2 and V3): the first after 8 weeks (± 1 week) from V0, the second after 8 weeks (± 1 week) from V1, and the third at the end of the study after 9 weeks (± 1 week) from V2 or in case of its premature termination of the study. The study received ethical approval.
Duration of treatment:	About 6 months
Statistical methods:	The calculation of the size was performed taking into account the following elements: - 1 ° type Alpha one-tailed error = 0.05; - 2nd type Beta error = 0.2; - dt = 0.80 (Δ expected between SLIT and placebo = 20%). Using this information, 165 subjects are needed (55 per group). Estimating a dropout rate of 15-20%, at least 192 subjects will have to be enrolled. It was assumed as a null hypothesis that there are no differences between the AUCs of the treatment groups. This hypothesis was verified by means of the Wilcoxon-Mann-Whitney-U-test. The null hypothesis was rejected and the superiority of the active treatment (pre-coseasonal and coseasonal) over placebo was confirmed if the p-value does not reach a significance level of 5%. Adverse Events were coded according to the MedDRA classification. The SOC (System Organ Class) and PT (Preferred Term) system will be used for the tabulation of the events. The difference in the number of patients with Adverse Events, Study Drug Related Adverse Events, Serious Adverse Events and Study Discontinuation Adverse Events in the three treatment arms will be assessed using the Chi-square test or the 2-tailed Fisher test.
Efficacy results:	Overall, 154 subjects were enrolled, 147 entered in the Safety Analysis Set, 141 in the Intention to Treat analysis: in SLIT pre-coseasonal group 48; in placebo pre-seasonal and SLIT co-seasonal 48, in placebo pre-co-seasonal 45. The number of males was 23 (44.2%) in the pre-co-seasonal SLIT group, 23 (45.1%) in the group placebo-preseasonal / SLIT-co-seasonal and 28 (54.9%) in the pre-coseasonal placebo group. The mean age (SD) of patients was 38.2 (10.7) years (range 18 - 60) in the pre-coseasonal SLIT group, 42.8 (11.2) years (range 18 - 60) in the pre-seasonal / SLIT placebo group co-seasonal and 39 (11.1) years (range 18 - 60) in the pre-co-seasonal placebo group.

	During the 2010 in the region Piemonte, the Parietaria pollen season started in week 15 (mid-April) and ended in week 39 (beginning-October); the average pollen counts never reached important peak levels: only week 17 (end-April) and 34-35-36 (end of August up to mid-September) reached at least a level >70 grans/m3. In the region Liguria and Sardinia, the season started in week 7 and ended in week 39; the average pollen counts reached important peak levels (>70 grans/m3) in weeks 13-14-15-16-17-19-20-21-22-23-25-26. Primary efficacy variable: A limited favorable trend was observed in favor of the active treatment for the median difference of -0.10 (95% IC: -1.13 to 1.15) between the pre-coseasonal SLIT and pre-coseasonal placebo groups, not reaching statistically significant difference with Wilcoxon-Mann-Whitney. In the ITT population, the median difference between the pre-seasonal placebo / coseasonal SLIT and pre-coseasonal placebo groups were 0.15 (95% IC: -0.86 to 1.41). Percentage of symptom-free days and symptomatic drug use: The mean percentage of symptom-free days and symptomatic drug use in the pre / coseasonal SLIT group is 32% in the V1-V2 period, 37.8% in the period V2-V3 and 33.7% in the total period (V1-V3). The mean percentage of symptomatic days and symptomatic drug use in the pre / coseasonal placebo group is 27% in the V1-V2 period, 35.8% in the period V2-V3 and 31.9% in the total period (V1-V3). The mean percentage of symptom-free days and symptomatic drug use in the pre-seasonal placebo / coseasonal SLIT group is 30.3% in the V1-V2 period, 40% in the period V2-V3 and 34.8% in the total period (V1-V3). As regards the Rhinasthma questionnaire on quality of life, in the Upper Airways domain and in the Global Summary the variations from V0 are positive and significantly different from zero to V2 for all three groups. In the Lower Airways and Respiratory Allergy Impact domains, no changes from V0 are significantly different from zero. The mean total compliance was 94.3 (range 77 - 102.9) in the pre / coseasonal SLIT group, 92 (range 48.3 - 100) in the pre-seasonal placebo / coseasonal SLIT group and 93.4 (range 61.8 - 103.6) in the pre / co-seasonal placebo group
Safety results:	The total number of adverse events during the study was 11 in the pre / coseasonal SLIT group, 21 in the pre-seasonal placebo / coseasonal SLIT group, and 8 in the pre / coseasonal placebo group. The number of patients with at least one adverse event is 5 (10.4%) in the pre / coseasonal SLIT group, 13 (25.5%) in the pre-seasonal placebo / coseasonal SLIT group and 7 (14.6%) in the pre / coseasonal placebo group. The difference between the treatment groups was not statistically significant. The main System Organ Classes involved (i.e. reported for at least 2% of patients in each group) are "Infections and infestations", 3 patients (6.25%) in the pre / co-seasonal SLIT group, 5 (9.8%) in the pre- seasonal / co-seasonal SLIT and 1 (2.08%) in the pre / co-seasonal placebo group, "Respiratory, thoracic and mediastinal disorders", 1 patient (2.08%) in the pre / co-seasonal SLIT group, 6 (11.8%) in the pre-seasonal placebo group / coseasonal SLIT and 1 (2.08%) in the pre / coseasonal placebo group.

	The total number of serious adverse events during the study is 1 (2.08%) in the pre / co-seasonal SLIT group. The number of patients with at least one serious adverse event is 1 (2.08%) in the pre / co-seasonal SLIT group. The difference between the treatment groups was not statistically significant. The only serious adverse event reported is "Knee sprain" reported by a patient of the pre / coseasonal SLIT group. The total number of adverse events leading to exit from the study is 1 (2.08%) in the pre / co-seasonal placebo group. The number of patients with at least one adverse event leading to exit from the study is 1 (2.08%) in the pre / co-seasonal placebo group. The difference between the treatment groups was not statistically significant. The only adverse event that leads to exit from the study reported is "Gastrointestinal Syndrome" reported by a patient of the pre / co-seasonal placebo group. The number of patients with at least one drug-related adverse event is 4 (7.84%) in the pre-seasonal placebo / coseasonal SLIT group. The difference between the treatment groups was statistically significant (p-value = 0.034). The main Preferred Term involved is "Asthma", 2 patients (3.92%) in the pre-seasonal placebo / cost-seasonal SLIT group.
Conclusion:	In this study, 154 patients were enrolled and no patients were screening failure. 154 patients were then randomized: 52 in the pre / coseasonal SLIT group, 51 in the pre-seasonal placebo / coseasonal SLIT group and 51 in the pre / coseasonal placebo group. However, 19 patients left the study prematurely: 8 patients (15.4% compared to the number of the related treatment group) in the pre / coseasonal SLIT group, 5 patients (9.8%) in the pre-seasonal placebo / coseasonal SLIT group and 6 patients (11.8%) in the pre / co-seasonal placebo group impairing the statistical power of the study. In addition, a number of subjects enrolled in the region Piemonte were exposed to a lower level of pollen counts in respect to those enrolled in the remaining two regions. Only limited trends of higher efficacy of the pre-coseasonal SLIT group in respect to the pre-coseasonal placebo group and the pre-seasonal placebo / coseasonal SLIT group were observed for the primary endpoint. Conversely, the percentage of symptom-free days and symptomatic drug use was the highest in the pre-seasonal placebo / coseasonal SLIT group. The treatment is overall safe and well tolerate. The frequency of subjects with adverse events is lower in the pre / coseasonal SLIT group. Starting active treatment coseasonally seems to be a little more associated to a higher risk of adverse events.