Clinical Trial Protocol

A randomized, double-blinded, parallel-group, placebo-controlled clinical study of the efficacy and safety of an oral nutraceutical (Lertal®) as an add-on to standard therapy for allergic rhinoconjunctivitis in pediatrics

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NAMES AND ADDRESSES

SCIENTIFIC COORDINATOR	Name:	Prof. Gian Luigi Marseglia
	Address:	Unità di Pediatria Generale e Specialistica Fondazione IRCCS – Policlinico San Matteo Università degli Studi di Pavia
SPONSOR	Company:	NTC – Novelty Technology Care
	Address:	Headquarters Via dei Gracchi, 35 20146 Milano
	Phone:	+39-02-43850436
CONTRACT RESEARCH ORGANIZATION	Company:	OPIS s.r.l.
	Address:	Palazzo Aliprandi Via Matteotti 10 20832 Desio (MB)
	Phone	+39-0362-6331

1 CLINICAL TRIAL SUMMARY

Title	A randomized, double-blinded, parallel-group, placebo-controlled clinical study of the efficacy and safety of an oral nutraceutical (Lertal®) as an add-on to standard therapy for allergic rhinoconjunctivitis in pediatrics.
Investigational sites	Approximately 17 centers in Italy.
Rationale and Aim of the study	Allergic rhinoconjunctivitis (AR) is a common chronic disorder in children, especially in developed countries. It is not characterized by nasal symptoms only (such as congestion and sneezing), but may also cause general complaints such as fatigue and cough. AR can also have detrimental effects on mood, sleep, social activities and scholastic performance. Treatment is usually pharmacological and includes decongestants, antihistamines and intranasal glucocorticosteroids. Aggressive therapy and the use of drugs with significant side effects should however be limited or avoided altogether in children. Nutraceuticals with proven efficacy may be associated with conventional therapy to speed up recovery, make it long lasting, and avoid aggressive therapeutic regimens or at least limit their duration. Lertal® is a novel nutraceutical containing seed extracts from *Perilla Frutescens*, Quercetin extracted from *Sophora japonica* and Vitamin D3, all compounds that have demonstrated their ability to reduce allergy symptoms and the use of anti-allergy drugs in adults. The purpose of this study is to evaluate the efficacy and safety of Lertal® as an add-on treatment for children affected by allergic rhinoconjunctivitis.
Study endpoints	**Primary end-point** To evaluate the change from baseline of the Total Symptom Score (TSS) after 4 weeks of treatment. **Secondary end-points** • Overall symptom control assessed by means of a VAS after 2 and 4 weeks of treatment • Change from baseline of the Total Symptom Score (TSS) after 2 weeks of treatment • Number of responders (30% reduction of TSS) after 2 and 4 weeks of treatment • Time to maximum effect on TSS vs placebo • Use of "rescue treatment" • Change from baseline of Total Nasal Symptom Score (TNSS) after 2 and 4 weeks of treatment

	• Change from baseline of Total Ocular Symptom Score (TOSS) after 2 and 4 weeks of treatment • Change from baseline of Total Throat Symptom Score (TTSS) after 2 and 4 weeks of treatment • Number of patients symptom-free or with mild symptoms during Period I • Issues interfering with quality of life at Baseline (Week 0), after Period I (Week 4) and after Period II (Week 8 o Week 16) • Number, intensity and duration of exacerbations during Period II. Exacerbations are defined as the need of an antihistamine medication of any kind, at any dose and of any duration
Type of study	Period I of the study is a 4-week randomized, double-blinded, parallel-group, placebo-controlled study. Period II is an open-label, controlled, parallel-group, extension study. This Period will use non-treatment as a control and will have a duration of: • 4 weeks for patients allergic to pollen • 12 weeks for patients allergic to dust mites
Duration of the study	The duration of the study, for each patient, is of approximately 10-18 weeks depending on the type of allergy.
Number of patients	160 patients are to be enrolled at about 17 sites located in Italy.
Study population	Pediatric patients with allergic rhinoconjunctivitis.
Inclusion criteria	• Age 6 to 12 years • Male or female • Diagnosis of allergic rhinoconjunctivitis • Hypersensitivity to dust mites or pollen confirmed with skin-prick test (wheal and redness, ≥ 3 mm more extended than control) performed in the previous 12 months • Total Symptoms Score (TSS) ≥ 15 and at least 1 for nasal congestion • Written informed consent of patient and of parent or legal guardian
Exclusion criteria	• Uncontrolled asthma • Secondary rhinitis to other causes • Documented evidence of acute or chronic sinusitis • Nasal polyps • Chronic or intermittent use of inhaled, oral, intramuscular, intravenous or topical corticosteroids • Use of leukotriene antagonists

	• Continuous use of antihistamines
	• Inadequate washout of drugs:
	  o Systemic or intranasal corticosteroids: 1 month
	  o Leukotriene antagonists: 1 month
	  o Sodium cromoglycate: 2 weeks
	  o Systemic or intranasal decongestants: 3 days
	  o Cetirizine, fexofenadine, loratadine, desloratadine, hydroxyzine: 5-10 days
	• Malformations of the nose, ear or throat
	• Upper or lower respiratory tract infection in the last 2 weeks
	• Participation in other clinical studies in the last month
	• Documented hypersensitivity to the study product or its excipients
	• Trip planned outside of the study area

Investigational product	Lertal® double-layer tablets Lertal® is a novel food supplement. Each tablet contains the following active ingredients: - Quercetin 150 mg: a natural flavonoid that inhibits the release of histamine, leukotrienes, PGD2, IL (IL-6, IL-8, TNF-alpha). - *Perilla frutescens* 80 mg: A dry extract of the seeds containing rosmarinic acid, luteolin, apigenin and crysoeriol that inhibits the release of histamine and expression of interleukins (IL-6, TNF-alpha). - Vitamin D3 5 mcg (200 IU), which contributes to the normal function of the immune system. **Period I** Patients will be randomized to one of the following two treatment groups: • One oral Lertal® tablet a day + standard therapy for 4 weeks. • One oral placebo tablet a day + standard therapy for 4 weeks. Standard therapy is an antihistamine chosen by the Investigator based on the clinical features of each patient. **Period II** • Patients taking Lertal® tablets in Period I continue taking one tablet a day for an additional 4 weeks (allergy to pollen) or 12 weeks (allergy to dust mites). Lertal® is not associated with standard therapy in Period II. • Patients taking placebo in Period I do not receive further

	treatment. A patient that concludes treatment Period I and still presents symptoms that do not permit interruption of standard therapy is considered a non-responder and will not take part in Period II of the study. The patient will be discontinued from the study and will be treated as deemed appropriate by the Investigator.
Comparator	In Period I: Placebo indistinguishable from study product + standard therapy (antihistamine).
Rescue treatment	Rescue therapy may be used as needed, and is defined as an increment of standard therapy (increase in dose, frequency of administration or change of antihistamine) in Period I, and as the use of any antihistamine in Period II. The use of rescue treatment will be recorded on the CRF and will be evaluated as efficacy variable.
Study design	❖ Run-in The 2-week run-in period consists of two visits: Visit 1 at Week -2 and Visit 2 at Week 0. During these visits, after having obtained signed informed consent from the patient, the Investigator will gather demographic and medical history data, perform a physical examination of the patients and evaluate their eligibility for the study according to inclusion/exclusion criteria. Eligible patients will then be randomized in a 1:1 ratio into two treatment groups and will be dispensed one of the study treatments: • Lertal® double-layer tablets (1 tab/day for 4 weeks) plus standard therapy (antihistamine) or • Lertal® placebo tablets (1 tab/day for 4 weeks) plus standard therapy (antihistamine). The randomization list will be stratified by type of allergy (pollen or dust mites). To ensure an adequate number of patients with both types of allergies (pollen and dust mites), the enrollment of patients with dust mite allergies will be blocked should these patients represent 60% of the study population before spring 2018. Baseline efficacy assessments of patient reported outcomes (PRO) will be collected at Visit 2 (Week 0). The patient will also be given a diary on which to record the use of rescue medication/concomitant medication and the occurrence of adverse events. The diary will also be used to record the occurrence/duration of exacerbations during Period II (need of an antihistamine medication of any kind, at any dose and of any duration). ❖ Period I Visit 3 (Week 2) and Visit 4 (Week 4) constitute the 4-week double-blinded

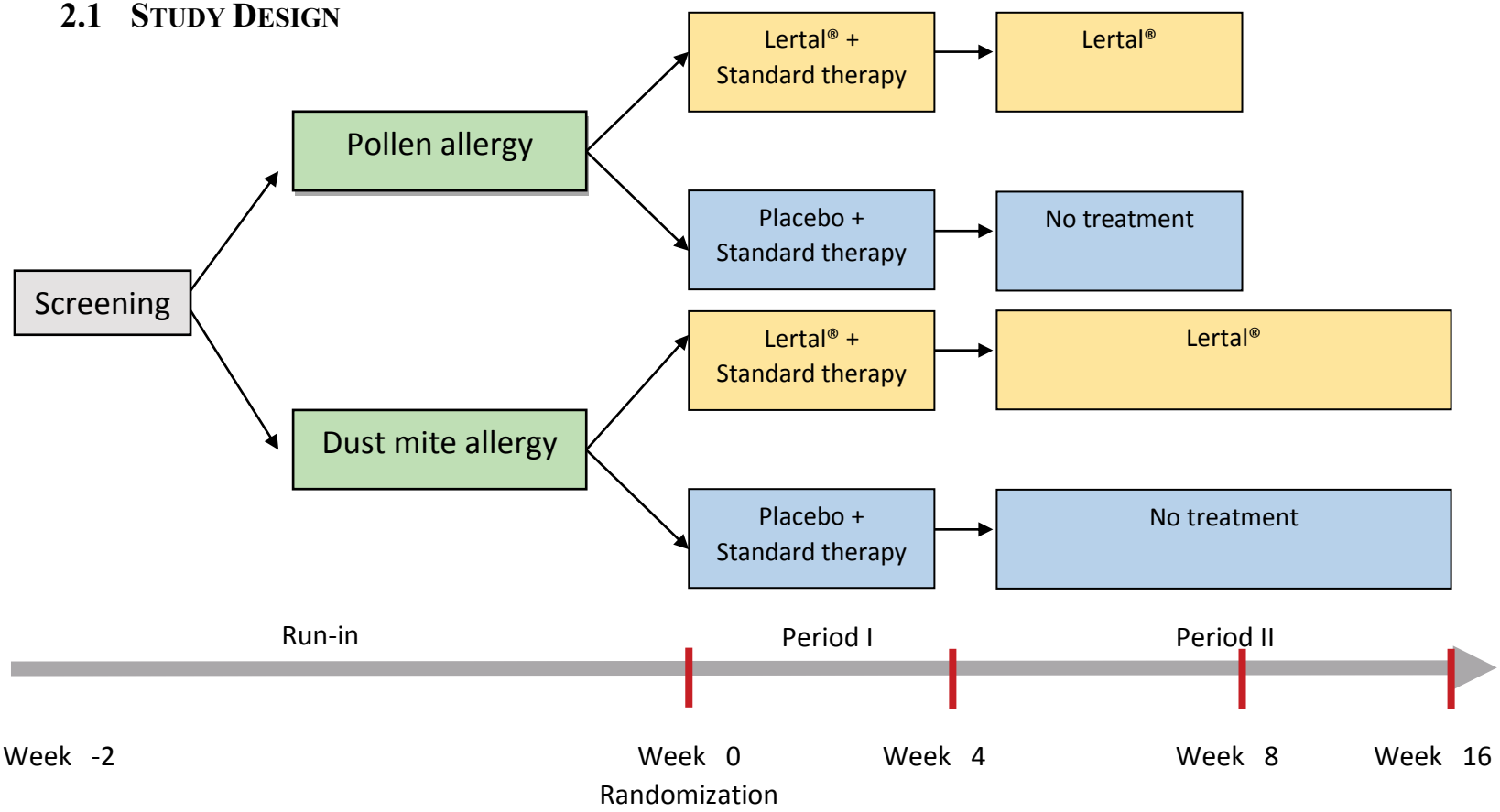
	treatment period (Period I). Visit 1 and Visit 2 may be performed on the same day. During these visits, patients will be asked to complete their questionnaires together with a parent and to return their diaries so information concerning safety (adverse events) and the use of rescue/concomitant medication can be collected. Patients need to return all unused product at both visits to check compliance with treatment. Once all data entry related to Period I has been completed (the Investigator has to certify that the data entered are complete and accurate), the eCRF will make the unblinding procedure available to the investigator so he or she can find out what treatment was taken by the patient during the double-blinded period. All assessments scheduled for Visit 4 shall be performed prior to unblinding. A patient that concludes treatment Period I and still presents symptoms that do not permit interruption of standard therapy is considered a non-responder and will not take part in Period II of the study. The patient will be discontinued from the study. ❖ Period II Period II is a 4-week (pollen allergy) or 12-week (dust mite allergy) open-label, parallel-group, extension study in which patients treated with study product in Period I continue treatment with Lertal® tablets, whereas patients initially treated with placebo receive no further treatment. Two visits, Visit 5 – Week 8 and Visit 6 – Week 16 (the latter only for patients with dust mite allergies) are scheduled during this period to collect efficacy, safety and quality of life data. Patients should return their diaries at these visits in order to collect data concerning exacerbations and or adverse events. Patients also need to return all unused product to check compliance with treatment.
Statistical considerations	• **Analysis populations** o Safety: All randomized patients who took at least one dose of study product. o Intention to treat (ITT): All randomized patients who took at least one dose of study product and have at least baseline and one post-baseline assessment of the primary efficacy variable. Patients who interrupt treatment will be considered as "failures" for qualitative variables and their missing quantitative data will be substituted according to the LOCF method (Last Observation Carried Forward). o Per protocol: All randomized patients who completed Period I and did not have significant protocol violations that regard inclusion/exclusion criteria or can condition the efficacy evaluation. The efficacy analysis will be performed on the ITT population and also on the PP population as a supportive analysis for the primary endpoint,

	whereas safety will be evaluated in the Safety population. • **Primary endpoint** Changes from baseline of TSS scores will be calculated after 4 weeks of treatment. The between-group analysis will be performed by means of a t-test for independent samples or analogous non-parametric test. • **Secondary endpoints** o Change from baseline of VAS score after 2 and 4 weeks of treatment. The between-group analysis will be performed using a t-test for independent samples or analogous non-parametric test. o Change from baseline of TSS scores after 2 weeks of treatment. The between-group analysis will be performed by means of a t-test for independent samples or analogous non-parametric test. o Change from baseline of TSS score for each patient after 2 and 4 weeks of treatment will be classified as ≥ 30% and < 30%, thus defining responder and non-responder patients. Between-group differences will be tested by means of a Chi-square test with 2x2 contingency tables. o Time to maximum effect on TSS vs placebo will be analysed by means of t-test for independent samples after log-transformation of the data or analogous non-parametric test. o Between-group differences in the number of patients using rescue treatment will be analyzed by means of a Chi-square test with 2x2 contingency tables. o Changes from baseline in TNSS, TOSS and TTSS scores will be calculated after 2 and 4 weeks of treatment and between-group differences analyzed using a t-test for independent samples or analogous non-parametric test. o The number of patients with score for a single symptom ≤ 1 will be calculated and the between-group differences analyzed by means of a Chi-square test with 2xn contingency tables, where n represents the number of observations. o The intensity of the onset of exacerbations occurring during Period II will be evaluated through the TTS score and compared between the two groups using a t-test for independent samples or analogous non-parametric test. o The between-group differences in number and duration of exacerbations occurring during Period II will be analyzed by means of a Mann-Whitney U test. • **Quality of life**

	Changes from baseline of the PRQLQ total score will be calculated at the end of Period I (Week 4) and end of Period II (Week 8 or Week16). An analysis of variance for repeated measures will be adopted, isolating the variability due to type of allergy, treatment group, time of observation and their interaction. • **Safety** Results of physical examinations at each assessment will be presented. The incidence of Adverse Events (AEs) and Serious Adverse Events (SAEs) recorded throughout the study will be presented overall and by treatment group respectively.

2 ASSESSMENT CHART

2.1 STUDY DESIGN



2.1 ASSESSMENT CHART

Study period	**Run-in***		**Period I (double-blinded)**		**Period II (follow-up)**	
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**
Time (weeks)	**-2**	**0**	**2**	**4**	**8**	**16**
Informed consent	X					
Inclusion/Exclusion criteria	X					
Demography/Medical history	X					
Physical examination	X	X		X	X	X
Randomization		X				
TSS, TNSS, TOSS, TTSS		X	X	X		
VAS		X	X	X		
PRQLQ		X		X	X	X
Incidence, intensity, and duration of exacerbations					X	X
Use of rescue medication			X	X	X	X
Provide/return diary		X	X	X	X	X
Dispensation of double blind treatment		X				
Dispensation of Lertal				X		
Concomitant treatment		X	X	X	X	X
Adverse Event monitoring		X	X	X	X	X
Product accountability			X	X	X	X

* Visit 1 and Visit 2 may take place on the same day.

3 TABLE OF CONTENTS

4 LIST OF ABBREVIATIONS

AE	Adverse Event
AR	Allergic Rhinoconjunctivitis
CRO	Contract Research Organization
EC	Ethics Committee
eCRF	Electronic Case Report Form
ITT	Intention To Treat
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
PRO	Patient Reported Outcome
PRQLQ	Pediatric Rhinoconjunctivitis Quality of Life Questionnaire
PP	Per Protocol
PT	Preferred Term
SAE	Serious Adverse Event
TNSS	Total Nasal Symptom Score
TOSS	Total Ocular Symptom Score
TSS	Total Symptom Score
TTSS	Total Throat Symptom Score
SOC	System Organ Class
VAS	Visual Analogue Scale
WHO	World Health Organization

Amendment No. 1 – July 12, 2017

Amendment rationale

This amendment of the protocol stems from enquiries and suggestions concerning protocol procedures arising during Investigator's meetings and provides details and clarification concerning the following items:

- Patient enrollment: To enroll enough patients allergic to pollen, the enrollment period has been extended to June 2018 to take advantage of the 2018 pollen season. The enrollment of patients with dust mite allergies will be blocked should these patients represent 60% of the study population before spring 2018.
- Patient evaluation at the end of Period I (Visit 4)
    - A patient that concludes treatment Period I and still presents symptoms that do not permit interruption of standard therapy is considered a *non-responder* and will not take part in Period II of the study. The patient will be discontinued from the study and will be treated as deemed appropriate by the Investigator.
    - To prevent study bias, it is reiterated that all assessments and eCRF completion scheduled for Visit 4 shall be performed prior to unblinding.
- Visit schedule: the amendment specifies that Visit 1 and Visit 2 may take place on the same day.

The amendment also provides additional details to the description of the statistical analyses and corrections of minor errors.

Changes to the protocol

Changes to specific sections of the protocol (and analogous sections of the synopsis) are shown in the track changes version of the protocol using strike through font for deletions and underlining for insertions.

Section 7.1 – Description of the protocol:

- Information is given on how non-responders in Period I must be handled.
- The amendment reiterates that all assessments scheduled for Visit 4 must be performed prior to unblinding.
- Visit 1 and Visit 2 may be performed on the same day.
- Randomization is stratified only by type of allergy (and not by center).

Section 8 – Selection of patients: the study will now be conducted at 17 centers instead of 16.

Section 9.1 – Investigational product: information concerning the handling of non-responders has been added.

Section 9.4 – Method of assigning patients to treatment group: additional information is provided about possibly blocking the enrollment of patients with dust mite allergies.

Section 9.9 – Treatment accountability and compliance: the amendment clarifies that patients will be asked to return unused tablets at Visit 3 and Visit 4 for Period I and at Visit 5 or Visit 6 for Period II (according to type of allergy).

Section 10.1.1 and 10.1.2 – Efficacy assessments: detail is provided concerning the calculation of TNSS, TOSS and TTSS scores.

Section 11.1 – Visit schedule: Visit 1 and Visit 2 may be performed on the same day is reiterated.

Section 11.2.2 – Permanent treatment discontinuation: information concerning the handling of non-responders has been added.

Section 13.2 – Statistical methods: minor additional details are provided regarding statistical methods.

This is a non-substantial amendment as it does not have a significant impact on the safety of the subjects, or the scientific value of the trial, or the conduct or management of the trial, or the quality or safety of the study treatment used in the trial. As such, the amendment will be sent to the competent Ethics Committees for notification.

5 INTRODUCTION AND RATIONALE

Allergic rhinoconjunctivitis (AR) is a common chronic disorder in children, especially in developed countries. It is not characterized by nasal symptoms only (such as congestion and sneezing) but may also cause general complaints such as fatigue and cough (1). AR can also have detrimental effects on mood, sleep, social activities and scholastic performance. Uncontrolled allergic rhinoconjunctivitis may aggravate the symptoms of asthma. Although classic "hay fever" is easily recognized in children who have a runny nose, sneezing, and itchy eyes during the pollen season, the diagnosis of allergic rhinoconjunctivitis is often missed in children with perennial nasal congestion.

The prevalence of allergic rhinoconjunctivitis has approximately doubled over the past 20 years (2). The prevalence of symptoms of rhinitis in children varies between countries, from 0.8% to 14.9% in 6-7 year olds and from 1.4% to 39.7% in 13-14 year olds. Environmental factors are probably responsible for these differences.

Treatment is usually pharmacological and includes decongestants, antihistamines and intranasal glucocorticosteroids. Aggressive therapy and the use of drugs with significant side effects should however be limited or avoided altogether in children.

Nutraceuticals with proven efficacy may be associated with conventional therapy to speed up recovery, make it long lasting, and avoid aggressive therapeutic regimens or at least limit their duration.

Lertal® is a novel nutraceutical containing seed extracts from *Perilla Frutescens*, Quercetin extracted from *Sophora japonica* and Vitamin D3.

The dry seed extract of Perilla frutescens contains rosmarinic acid and other flavonoids, such as luteolin, apigenin and crysoeriol, and has shown *in vivo* and *in vitro* anti-allergic activity mediated by inhibition of the release of histamine and expression of interleukins (IL-6, TNF-alpha) (3,4,5,6). This activity was demonstrated in a clinical study that showed a significant reduction in clinical symptoms and in the number of neutrophils and eosinophils in the nasal fluid of seasonal allergic rhinoconjunctivitis patients compared to placebo. Perilla also has significant inhibitory activity against both 5-lipoxygenase and 12-lipoxygenase, key enzymes in one of the pathways of allergy and inflammation (7).

Quercetin is a bioflavonoid found in red wine, grapefruit, onions, apples, black tea, and, in lesser amounts, in leafy green vegetables and beans (8). Quercetin has a strong affinity for mast cells and basophils and tends to stabilize their cell membranes and block degranulation, thereby preventing them from spilling pro-inflammatory, allergy-symptom-causing histamine/serotonin into the surrounding blood and tissue in response to IgE antibody.

Vitamin D3 is important for its contribution to the normal function of the immune system, as shown in a number of studies (9-10).

Lertal® is formulated in bilayer tablets composed of a fast-release layer that allows the rapid antihistamine activity of Perilla, and a sustained-release layer that enhances Quercetin and Vitamin D3 bioavailability and anti-allergy activity spread over time.

A recent clinical study enrolled 23 subjects with at least a one-year history of allergic rhinitis and a positive skin prick test or RAST to Parietaria officinalis pollen. At baseline, the subjects had symptoms of nasal and/or ocular seasonal allergic rhinitis. The comparison of the scores obtained in the two visits (baseline and final) showed a highly significant reduction of the overall symptoms and a reduction in the consumption of anti-allergic drugs. No noteworthy side effect was recorded and all patients finished the study with good compliance (11).

The purpose of this study is to evaluate the efficacy and safety of Lertal® as an add-on treatment for children affected by allergic rhinoconjunctivitis.

6 STUDY OBJECTIVES

6.1 PRIMARY

The primary objective of the study is to evaluate the effect of Lertal® as add on therapy in pediatric patients with allergic rhinoconjunctivitis, using Total Symptom Score (TSS) as primary variable. The primary endpoint of this study is the change from baseline of the TSS after 4 weeks of treatment.

6.2 SECONDARY

The secondary objective is to evaluate efficacy, safety and quality of life in pediatric patients with allergic rhinoconjunctivitis treated with Lertal®. The secondary endpoints are the following:

- Overall symptom control assessed by means of a VAS after 2 and 4 weeks of treatment.
- Change from baseline of the Total Symptom Score (TSS) after 2 weeks of treatment.
- Number of responders (at least 30% reduction of TSS) after 2 and 4 weeks of treatment.
- Time to maximum effect on TSS vs placebo.
- Use of “rescue treatment.”
- Change from baseline of Total Nasal Symptom Score (TNSS) after 2 and 4 weeks of treatment.
- Change from baseline of Total Ocular Symptom Score (TOSS) after 2 and 4 weeks of treatment.
- Change from baseline of Total Throat Symptom Score (TTSS) after 2 and 4 weeks of treatment.

- Issues interfering with quality of life at Baseline (Week 0), after Period I (Week 4) and after Period II (Week 8 o Week 16).
- Number of patients symptom-free or with mild symptoms during Period I.
- Number, intensity and duration of exacerbations during Period II. Exacerbations are defined as the need of an antihistamine medication of any kind, at any dose and of any duration.

7 STUDY DESIGN

7.1 DESCRIPTION OF THE PROTOCOL

❖ Run-in

The 2-week run-in period consists of two visits: Visit 1 at Week -2 and Visit 2 at Week 0. Visit 1 and Visit 2 may be performed on the same day During these visits, after having obtained signed informed consent from the patient, the Investigator will gather demographic and medical history data, perform a physical examination of the patients and evaluate their eligibility for the study according to inclusion/exclusion criteria indicated in Section 8. Eligible patients will then be randomized in a 1:1 ratio into two treatment groups and will be dispensed one of the study treatments:

- Lertal® double-layer tablets (1 tab/day for 4 weeks) plus standard therapy (antihistamine).

or

- Lertal® placebo tablets (1 tab/day for 4 weeks) plus standard therapy (antihistamine).

The randomization list will be stratified by type of allergy (pollen or dust mites).

Baseline assessments of patient reported outcomes (PRO) will be collected at Visit 2 (Week 0). The patient will also be given a diary on which to record the use of rescue medication/concomitant medication and the occurrence of adverse events. The diary will also be used to record the occurrence/duration of exacerbations during Period II (need of an antihistamine medication of any kind, at any dose and of any duration).

❖ Period I

Visit 3 (Week 2) and Visit 4 (Week 4) constitute the 4-week double-blinded treatment period (Period I). During these visits, patients will be asked to complete their questionnaires and to return their diaries so information concerning safety (adverse events) and the use of rescue/concomitant medications can be collected. Patients need to return all unused product at both visits to check compliance with treatment. Once all data entry related to Period I has been completed (the Investigator has to certify that the data entered are complete and accurate), the eCRF will make the unblinding procedure available to the investigator so he or she can find out what treatment was

taken by the patient during the double-blinded period. All assessments scheduled for Visit 4 shall be performed prior to unblinding.

A patient that concludes treatment Period I and still presents symptoms that do not permit interruption of standard therapy is considered a non-responder and will not take part in Period II of the study. The patient will be discontinued from the study.

❖ Period II

Period II is a 4-week (pollen allergy) or 12-week (dust mite allergy) open-label, parallel-group, extension study in which patients treated with study product during Period I continue treatment with Lertal® tablets, whereas patients initially treated with placebo receive no further treatment. Two visits, Visit 5 – Week 8 and Visit 6 – Week 16 (the latter only for patients with dust mite allergies) are scheduled during this period to collect efficacy, safety and quality of life data. Patients should return their diaries at these visits in order to collect data concerning exacerbations and or adverse events. Patients also need to return all unused product to check compliance with treatment.

See Section 2 for a graph of the study design and a table of what assessments are to be carried out and when. See Section 10 for a description of the assessments.

7.2 Duration of Study Participation

7.2.1 Duration of study participation for each patient

The study for each participant will last approximately 10 weeks for patients allergic to pollen and 18 weeks for patients allergic to dust mites.

7.2.2 Determination of end of clinical trial (all patients)

The study will end with the last visit of the last patient.

8 Selection of Patients

The study population will be made up of children affected by allergic rhinoconjunctivitis. The study will be conducted at approximately 17 sites located in Italy.

8.1 Inclusion Criteria

Each patient must meet all of the following inclusion criteria:

- Age 6 to 12 years
- Male or female
- Diagnosis of allergic rhinoconjunctivitis

- Hypersensitivity to dust mites or pollen confirmed with skin-prick test (wheal and redness, ≥ 3 mm more extended than control) performed in the previous 12 months
- Total Symptoms Score (TSS) ≥ 15 and at least 1 for nasal congestion
- Written informed consent of patient and of parent or legal guardian

8.2 EXCLUSION CRITERIA

Each patient must meet none of the following exclusion criteria:

- Uncontrolled asthma
- Secondary rhinitis to other causes
- Documented evidence of acute or chronic sinusitis
- Nasal polyps
- Chronic or intermittent use of inhaled, oral, intramuscular, intravenous or topical corticosteroids
- Use of leukotriene antagonists
- Continuous use of antihistamines
- Inadequate washout of drugs:
    - Systemic or intranasal corticosteroids: 1 month
    - Leukotriene antagonists: 1 month
    - Sodium cromoglycate: 2 weeks
    - Systemic or intranasal decongestants: 3 days
    - Cetirizine, fexofenadine, loratadine, desloratadine, hydroxyzine: 5-10 days
- Malformations of the nose, ear or throat
- Upper or lower respiratory tract infection in the last 2 weeks
- Participation in other clinical studies in the last month
- Documented hypersensitivity to the study product or its excipients
- Trip planned outside of the study area

9 STUDY TREATMENTS

9.1 INVESTIGATIONAL PRODUCT

Lertal® double-layer tablets

Lertal® is a novel food supplement. Each tablet contains the following active ingredients in a double-layer "fast-slow" release tablets:

- Quercetin 150 mg: a natural flavonoid that inhibits the release of histamine, leukotrienes, PGD2, IL (IL-6, IL-8, TNF-alpha).
- *Perilla frutescens* 80 mg: A dry extract of the seeds containing rosmarinic acid, luteolin, apigenin and crysoeriol that inhibits the release of histamine and expression of interleukins (IL-6, TNF-alpha).
- Vitamin D3 5 mcg (200 IU), which contributes to the normal function of the immune system.

One oral Lertal® tablet a day is to be administered together with standard therapy (antihistamine) for 4 weeks by patients randomized to the active treatment group + standard therapy during Period I. During Period II, patients taking Lertal® tablets in Period I continue taking one tablet a day for an additional 4 weeks if allergic to pollen or 12 weeks if allergic to dust mites. Lertal® is not associated with standard therapy during Period II.

A patient that concludes treatment Period I and still presents symptoms that do not permit suspension of standard therapy is considered a non-responder and will not take part in Period II of the study. The patient will be discontinued from the study and will be treated as deemed appropriate by the Investigator.

Lertal® will be provided by the Sponsor free of charge.

9.2 PLACEBO

One placebo tablet identical in appearance, size and taste to Lertal® tablets is to be administered daily together with standard therapy (antihistamine) by patients randomized to the placebo + standard treatment group for 4 weeks (Period I only). In Period II, patients taking placebo tablets in Period 1 receive no further treatment.

9.3 STANDARD TREATMENT

Standard therapy is an antihistamine chosen by the Investigator based on the clinical features of each patient and is to be used for 4 weeks (Period I) by patients of both treatment groups.

9.4 METHOD OF ASSIGNING PATIENTS TO TREATMENT GROUP

For Period I, patients will be randomized with a 1:1 ratio to one of the two treatments (oral Lertal® tablets +standard therapy or placebo tablets + standard therapy).

The study product and placebo will be provided in identical boxes and will be identified with a four-digit box number.

The randomization list will be stratified by type of allergy and generated according to permutated blocks codes by an independent statistician through a validated SAS program ® Software Version 9.4.

The randomization process will be centralized and the assignment to one of the treatments will be carried out through the web-based Electronic Case Report Form (eCRF) system by designated site personnel. When a patient is considered eligible (i.e. he/she fulfils all the inclusion criteria and does not present any exclusion criteria of the Study Protocol), site personnel will access the system in a dedicated section, using a personal account to receive the box number for the incoming patient and will confirm the assignment into the system. Each box number is linked to a treatment code through the randomization list.

A randomized patient is defined as a patient who is registered and is assigned to a box number by the eCRF.

To ensure an adequate number of patients with both types of allergies (pollen and dust mites), the enrollment of patients with dust mite allergies will be blocked should these patients represent 60% of the study population before spring 2018.

9.5 BLINDING PROCEDURES

9.5.1 Methods of blinding

Patients, investigator staff, personnel performing the study assessments and data analysts will remain blinded to the identity of the treatment from the time of randomization until the end of Period I using the following methods:

1. The two treatments will be identical in packaging, labeling, administration schedule, appearance, taste and odor.
2. Randomization data will be kept strictly confidential until the time of unblinding and will not be accessible by anyone involved in the study.

Unblinding will occur only in case of patient emergencies and at the end of Period I. Health authorities will be granted access to unblinded data if needed.

9.5.2 Randomization code breaking during the study

In case of an adverse event (AE), the code should only be broken in circumstances when knowledge of the treatment is required for treating the patient.

The code can be broken at any time through the eCRF system. If the blind is broken, the Investigator should document the date, time of day, and reason for code breaking.

Any patient whose treatment code has been broken inadvertently or for any non-emergency reason will be discontinued from the trial.

9.6 PACKAGING AND LABELING

Each box of Lertal® (and placebo) contains 2 foil blisters each containing 15 tablets. The content of the labeling will be in accordance with local regulatory specifications and requirements.

9.7 STORAGE CONDITIONS AND SHELF LIFE

The Principal Investigator or other authorized persons (pharmacists) are responsible for storing the product in a secure and safe place in accordance with local regulations, labeling specifications, policies, and procedures.

9.8 RESPONSIBILITIES

The Investigator, the hospital pharmacist, or other personnel allowed to store and dispense the product will be responsible for ensuring that it is securely maintained as specified by the Sponsor and in accordance with applicable regulatory requirements.

The Investigator will be responsible for ensuring that an accurate record of the product issued and returned is maintained.

Any quality issue detected upon receipt of the product (condition, appearance, documentation, labeling, expiration date, etc.) should be promptly notified to the Sponsor.

9.9 TREATMENT ACCOUNTABILITY AND COMPLIANCE

Patients will be asked to return all unused tablets at Visit 3 and Visit 4 for Period I and at Visit 5 or 6 for Period II (according to type of allergy). Compliance will be assessed by counting unused tablets. A subject Treatment Accountability Log for dispensed and returned treatment will be kept for each patient.

The Investigator will be responsible for ensuring that an accurate record of the treatment issued and returned is maintained through a Site Treatment Accountability Log. Destruction of all study products (used or unused) shall be carried out following the Sponsor's written authorization.

9.10 RESCUE AND CONCOMITANT MEDICATION

Rescue therapy may be used as needed, and is defined as an increment of standard therapy (increase in dose, frequency of administration or change of antihistamine) in Period I, and as the use of any antihistamine in Period II. The use of rescue treatment will be recorded on the CRF and will be evaluated as efficacy variable.

The following medications are prohibited during the study:

- Systemic or intranasal corticosteroids
- Leukotriene antagonists
- Sodium cromoglycate

10 ASSESSMENTS

10.1 EFFICACY ASSESSMENTS

10.1.1 Total Symptom Score

The primary variable of the study is the Total Symptoms score (**TSS**), a patient-reported evaluation of nine symptoms:

- Nasal symptoms (**TNSS**): itching, sneezing, rhinorrhea, nasal congestion
- Ocular symptoms (**TOSS**): itching, hyperemia of conjunctiva, tearing
- Throat symptoms (**TTSS**): itching, coughing

With the help of their parents, patients will score symptoms on a 4-point scale: 0 = absent or irrelevant, 1 = mild, 2 = moderate, 3 = severe.

TNSS is the sum of the scores of nasal symptoms, TOSS the sum of the scores of ocular symptoms and TTSS the sum of throat symptoms.

TSS is calculated as the sum of TNSS, TOSS and TTSS.

At baseline (Visit 2), Visit 3 and Visit 4, and with the help of a parent, patients are asked to assign a score to the symptoms experienced in the last 12 hours and over the previous two weeks.

The overall TSS score is derived as the mean of the two TSS scores related to the symptoms experienced in the last 12 hours and over the previous two weeks.

10.1.2 TNSS, TOSS, TTSS

Total Nasal Symptom Score (TNSS), Total Ocular Symptom Score (TOSS) and Total Throat Symptom Score will be evaluated singularly as described for TSS.

The overall TNSS, TOSS and TTSS scores are derived as the mean of the two TNSS, TOSS and TTSS scores related to the symptoms experienced in the last 12 hours and over the previous two weeks.

10.1.3 Visual Analogue Scale (VAS)

At Visit 2, Visit 3 and Visit 4 (Period I) the patient will be asked to indicate overall system distress on a 100 mm Visual Analogue Scale (VAS) were 0 is equal to no discomfort and 100 the worst possible discomfort.

10.1.4 Pediatric Rhinoconjunctivitis Quality of Life Questionnaire (PRQLQ)

The PRQLQ consists of 23 questions in 5 domains (nasal symptoms, ocular symptoms, practical issues, limitation of activities, other symptoms), that are answered on a 7-point scale (0-6), where 0 represents the absence of problems and 6 the greatest symptom distress. Children will complete the questionnaire at baseline and at the end of Period I (Visit 4) and at the end of Period II (Visit 5 or Visit 6). Since parents often have a poor perception of the problems that their child experiences

as a result of their illness, it should be the child who responds to the questions - never the parent or caregiver. Parents should wait in another room to prevent the child looking to the parent for guidance and to stop the parent telling the child how to respond or challenging the child's own response.

10.1.5 Use of rescue medication

Patients will be asked to report the use of any rescue medication during periods I and II of the study.

10.1.6 Patient diary

Children will be given a diary and asked, together with a parent, to write down any rescue medication/concomitant medications taken, as well as the occurrence of any adverse events. During Period II, the number and duration of any exacerbations (need of an antihistamine medication of any kind, at any dose and of any duration) should be indicated in the diary.

10.2 SAFETY

Safety will be assessed on the incidence of adverse events for each treatment and on physical examinations.

10.2.1 Adverse events

An adverse event (AE) is as any untoward medical occurrence in a patient administered the product and which does not necessarily have to have a causal relationship with the treatment.

A **serious adverse event** (SAE) is any untoward medical occurrence that at any dose:

- Results in death, or
- Is life-threatening, or
- Requires inpatient hospitalization or prolongation of existing hospitalization, or
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect, or
- Is a medically important event.

Should an SAE occur, the Investigator or any designees must send the signed and dated corresponding SAE form by fax or e-mail within 24 hours to the pharmacovigilance officer whose name, fax number, and e-mail address appear below.

CRO Pharmacovigilance Officer: Dr Riccardo Chisci, OPIS s.r.l. Email: all_phv@opis.it Fax: +39 0362 633622 Tel: +39 0362 633312 Mobile: +39 348 6440813

The Investigator should take appropriate measures to follow all AEs until clinical recovery is complete and laboratory results have returned to normal, or until progression has been stabilized to ensure the safety of the patients. This may imply that observations will continue beyond the last planned visit per protocol, and that additional investigations may be requested by the monitoring team.

10.2.2 Physical examination

A Physical examination of the patient will be performed at both visits of the run-in period (Visit 1 and Visit 2), and at the end of periods I and II (Visit 4 and Visit 5 or 6).

10.3 COMPLIANCE

Patients will be asked to return any unused treatment at Visit 3, Visit 4 and Visit 5 or 6 and adherence to treatment will be evaluated by counting the number of unused tablets.

11 STUDY PROCEDURES

11.1 VISIT SCHEDULE

The visit schedule consists of 6 visits. V1 and V2 (baseline) take place during the run-in period, V3 and V4 during the 4 weeks of Period I, and V5 and V6 (only for patients allergic to dust mites) during the 4 weeks or 12 weeks (only for patients allergic to dust mites) of Period II.

At V1 (Week -2), after having obtained signed informed consent from the patient, the Investigator will gather demographic and medical history data. The Investigator will perform a physical examination and evaluate the patient's eligibility for the study according to the inclusion/exclusion criteria indicated in Section 8.

At V2 (Week 0), each patient will be randomized to one of two treatments (Lertal® + standard therapy or placebo + standard therapy) and will be provided with enough product to last until Visit 4. The Investigator will perform a physical examination, and the patient will be asked to complete the patient reported outcomes (TSS, TNSS, TOSS, TTSS, VAS, PRQLQ). The Investigator will also enquire about any adverse events the patient may have experienced and about any concomitant medication the patient may have taken since Visit 1. The patient will be given a diary.

Visit 1 and Visit 2 may be performed on the same day.

V3 (Week 2), V4 (Week 4): The patient will be asked to complete the patient reported outcomes (TSS, TNSS, TOSS, TTSS, PRQLQ, VAS) and the Investigator will also enquire about any adverse events the patient may have experienced and about any rescue/concomitant medication the patient may have taken since the previous visit. A physical exam will be performed at V4. The diary should be returned at these visits for review by the Investigator. The patient should also return unused product at each visit.

V5 (Week 8), V6 (Week 16 – only for patients allergic to dust mites): The patient will be asked to complete the quality of life questionnaire (PRQLQ) and the Investigator will also enquire about any adverse events/exacerbations the patient may have experienced and about any rescue/concomitant medication the patient may have taken since the previous visit. A physical exam will be performed at V5 or V6. The diary should be returned at these visits for review by the Investigator.

See the assessment chart in Section 2.2 for details regarding the visit schedule and assessments and Section 10 for information concerning the assessments.

11.2 TEMPORARY OR PERMANENT TREATMENT/STUDY DISCONTINUATION

Patients should continue using the product whenever possible and permanent discontinuation should be only a last resort. Any treatment discontinuation should be fully documented on the eCRF.

11.2.1 Temporary treatment discontinuation

Temporary treatment discontinuation may be considered by the Investigator because of a suspected AE. Treatment can be resumed under close clinical monitoring once the Investigator has considered an association of the treatment with the occurrence of the event unlikely and if the selection criteria for the study are still met (refer to Section 8).

The duration of all temporary treatment discontinuations should be recorded by the Investigator in the eCRF.

11.2.2 Permanent treatment discontinuation

The patients may withdraw from treatment at any time and irrespective of the reason, or this may be the Investigator's decision. A patient that concludes treatment Period I and still presents symptoms that do not permit interruption of standard therapy is considered a *non-responder* and will be discontinued from the study. All efforts should be made to document the reasons for treatment discontinuation on the eCRF. Discontinued patients will not be replaced.

11.2.3 Handling of patients after permanent treatment discontinuation

Patients will be followed-up according to the study procedures as specified in this protocol up to the scheduled date of study completion, or up to recovery or stabilization of any AE, whichever comes last.

If possible, and after the permanent discontinuation of treatment, the patients will be assessed using the procedures normally planned for the last visit.

All cases of permanent treatment discontinuation should be recorded by the Investigator in the CRF when considered as confirmed.

For patients who fail to return to the site, the Investigator should make the best effort to re-contact the patient's parents and to determine their child's health status. Attempts to contact such patients must be documented in the patient's records.

12 DATA MANAGEMENT

12.1 DATA COLLECTION

Designated Investigator staff will enter the data required by the protocol onto the Electronic Case Report Forms using fully validated software that conforms to 21 CFR Part 11 requirements. Designated Investigator site staff will not be given access to the EDC system until they have been trained.

Web based software will be used: no installation procedure will be needed. Investigator site qualified personnel will be allowed to access to the eCRF by means of a 'login mask' requiring Username and Password, and it will be possible to read, modify and update only the information reported at his/her site. Each page should report site code and patient code.

The Investigator must certify that the data entered onto the Electronic Case Report Forms are complete and accurate.

12.2 DATA MANAGEMENT AND QUALITY CONTROL

The Data Manager of the Contract Research Organization (CRO) working on behalf of the Sponsor will review the data entered onto the eCRFs by investigational staff for completeness and accuracy, and will instruct the site personnel to make any required corrections or additions. He/she will perform the cleaning session reviewing the warning messages raised by on-line checks and by running post-entry checks by means of validation programmes and data listings specific for the study. During this process, if clarification is needed, the Data Manager will raise queries by means of data query forms through the WEB application. Designated Investigator site staff is required to respond to the query and the Data Manager will make the correction to the database on the basis of the query response.

The Data collection and the Queries flow as well as the on-line and off-line control checks will be detailed in the Data Management Plan and Data Validation documents.

Concomitant medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

The occurrence of any protocol deviations will be determined. After these actions have been completed and the database has been declared to be completed and accurate, it will be locked and made available for data analysis. Any changes to the database after that time can only be made upon documented agreement within the Study Team.

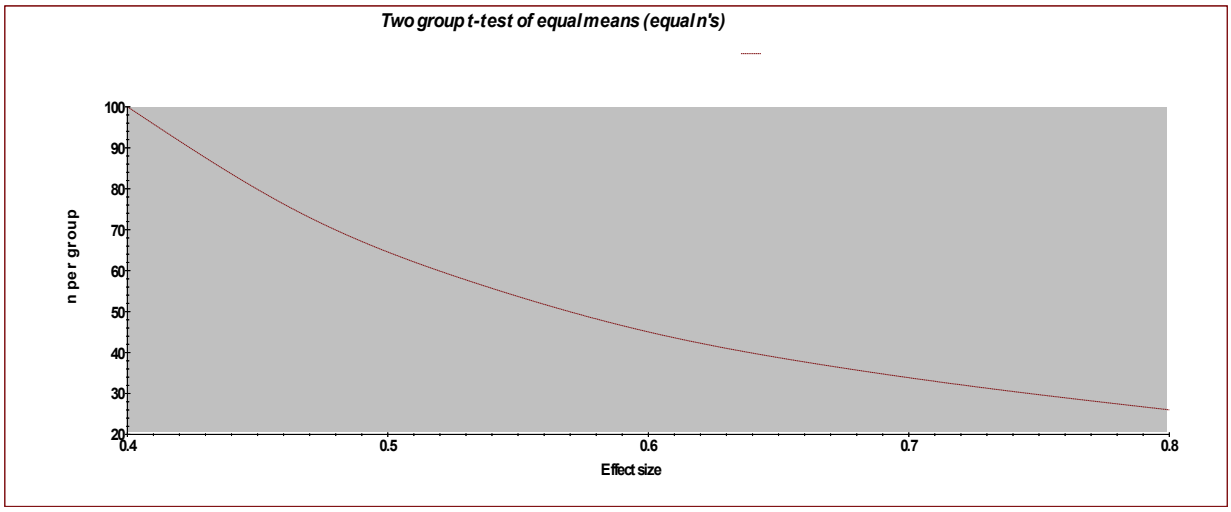
13 STATISTICAL CONSIDERATIONS

13.1 DETERMINATION OF SAMPLE SIZE

160 patients are to be enrolled in this study.

A sample of 72 patients for each group will have an 80% power to detect an effect size on the primary variable ($\delta = |\mu_1 - \mu_2| / \sigma$) of 0.47 (medium effect size) (12), using an independent samples t-test with a two-tailed significance level of 5%.

A sample size of 80 patients per group will account for an expected dropout rate of 12% (13), using Freedman's formula (*Control Clin Trials, 1990*): n'= 100*n/100-x, where x is the expected dropout rate.



13.2 STATISTICAL METHODS

13.2.1 Analysis populations

Patients without a valid or adequately obtained Informed Consent Form (ICF) will be excluded from any analysis population.

The following analysis populations have been defined for these statistical analyses:

- Safety: All randomized patients who took at least one dose of study product.
- Intention to treat (ITT): All randomized patients who took at least one dose of study product and have at least baseline and one post-baseline assessment of the primary efficacy variable. Patients who interrupt treatment will be considered as "failures" for qualitative variables and their missing quantitative data will be substituted according to the LOCF method (Last Observation Carried Forward).
- Per protocol (PP): All randomized patients who completed Period I and did not have significant protocol violations that regard inclusion/exclusion criteria or can condition the efficacy evaluation.

The efficacy analysis will be performed on the ITT population and also on the PP population as a supportive analysis for the primary endpoint and reported overall and by planned treatment group. Safety will be evaluated in the Safety population and reported overall and by actual treatment group.

13.2.2 Statistical Analysis

All data collected in the study will be listed and summarized as appropriate as described below. Continuous data will be summarized by means of common descriptive statistics: mean, standard deviation (SD), median, first and third quartiles, minimum and maximum. Categorical data will be presented by absolute and relative frequencies (n and %) or contingency tables.

For the safety analysis, patients will be included in based on available assessments; no missing data handling approach will be applied. For efficacy analyses, patients who interrupt treatment will be considered as "failures" for qualitative variables and their missing quantitative data will be substituted according to the LOCF method (Last Observation Carried Forward). Unless stated otherwise, two-sided p-values <0.05 will be considered statistically significant.

All statistical tables, listings, figures and analyses will be generated using SAS® release 9.4 or later (SAS Institute Inc., Cary NC, USA).

No interim analyses are planned.

Further details about data analysis will be provided in the Statistical Analysis Plan document.

All data about patient demographics and baseline characteristics will be summarized on the ITT population by treatment group by means of summary descriptive statistics.

The number and percentages of subjects meeting all eligibility criteria at screening will be provided. The analysis populations will be described and the reasons for excluding a patient from any particular population will be provided with the number of protocol deviators per each criterion.

A complete description of patients' disposition will be provided specifying the number of randomized patients, the number of patients at each visit, the number of completed and discontinued patients and the reason for the discontinuation.

Medical history data will be presented by Medical Dictionary for Regulatory Activities MedDRA dictionary system organ class (SOC) and preferred term (PT).

Concomitant medications and significant non-drug therapies will be presented by WHO Drug Dictionary ATC class and preferred term.

- **Primary endpoint**

Changes from baseline of TSS scores will be calculated after 4 weeks of treatment. The between-group analysis will be performed by means of a t-test for independent samples or analogous non-parametric test.

- **Secondary endpoints**
    - Change from baseline of VAS score after 2 and 4 weeks of treatment. The between-group analysis will be performed by means of a t-test for independent samples or analogous non-parametric test.

- Changes from baseline of TSS scores after 2 weeks of treatment. The between-group analysis will be performed by means of a t-test for independent samples or analogous non-parametric test.
- Changes from baseline of TSS score for each patient after 2 and 4 weeks of treatment will be classified as ≥ 30% and < 30%, thus defining responder and non-responder patients. Between-group differences will be tested by means of a Chi-square test with 2x2 contingency tables.
- Time to maximum effect on TSS vs placebo will be analysed by means of t-test for independent samples after log-transformation of the data or analogous non-parametric test.
- Between-group differences in the number of patients using rescue treatment will be analyzed by means of a Chi-square test with 2x2 contingency tables.
- Changes from baseline in TNSS, TOSS and TTSS scores will be calculated after 2 and 4 weeks of treatment and between-group differences analyzed by means of a t-test for independent samples or analogous non-parametric test.
- The number of patients with score for a single symptom ≤ 1 will be calculated and the between-group differences analyzed by means of a Chi-square test with 2xn contingency tables, where n represents the number of observations.
- The intensity of the onset of exacerbations occurring during Period II will be evaluated through the TTS score and compared between the two groups using a t-test for independent samples or analogous non-parametric test.
- The between-group differences in the number and duration of exacerbations occurring during Period II will be analyzed by means of a Mann-Whitney U test.

- **Quality of life**

Changes from baseline of the PRQLQ total score will be calculated at the end of Period I (Week 4) and end of Period II (Week 8 or Week16). An analysis of variance for repeated measures will be adopted, isolating the variability due to type of allergy, treatment group, time of observation and their interaction.

- **Safety**

All safety analyses will be performed on the Safety set. No missing data handling approach will be applied.

Results of physical examinations at each assessment will be presented.

The incidence of Adverse Events (AEs) and Serious Adverse Events (SAEs) recorded throughout the study will be presented overall and by treatment group respectively.

According to the onset date of the event, AEs will be defined as follows:

- treatment-emergent AE, those events with an onset date after any treatment initiation
- non-treatment-emergent AE, those events with an onset date between informed consent and any treatment initiation

Nontreatment-emergent AEs will be listed only.

Treatment-emergent AEs will be summarized by MedDRA dictionary system organ class and preferred term. A summary of treatment-emergent AEs by preferred term and severity will be also provided. All related treatment-emergent AEs, treatment-emergent AEs with an outcome of death, treatment-emergent AEs leading to discontinuation of treatment will be summarized by MedDRA dictionary system organ class and preferred term and will also be listed. Serious treatment-emergent AEs will be summarized similarly.

All deaths occurred will be listed together with all their details.

14 ETHICAL AND REGULATORY CONSIDERATIONS

14.1 ETHICAL AND REGULATORY STANDARDS

This clinical trial will be conducted by the Sponsor, the Investigator, delegated Investigator staff and Sub-investigator in accordance with the principles laid down by the 18th World Medical Assembly (Helsinki, 1964) and all applicable amendments, applicable provisions of ICH guidelines for good clinical practice (ICH-GCP), and all applicable laws and regulations.

14.2 INFORMED CONSENT

The Investigator, or a person designated by the Investigator, shall inform the patient of all the aspects of the clinical trial to the fullest extent possible, and in language and terms they are able to understand, including the written information giving approval/favorable opinion by the Ethics Committee (EC).

Prior to a patient's participation in the clinical trial, the written informed consent form shall be signed and personally dated by the patient and by the person who conducted the informed consent discussion. A copy of the signed and dated written informed consent form will be given to the patient.

The informed consent form must be reviewed and approved by the Sponsor prior to submission to the EC for approval/favorable opinion.

14.3 INDEPENDENT ETHICS COMMITTEE (EC)

The Investigator or the Sponsor must submit this clinical trial protocol to the appropriate EC as per local regulations, and is required to forward to the other party a copy of the dated approval/favorable opinion signed by the Chairman with EC composition.

The clinical trial (study number, protocol title and version number), the documents reviewed (clinical trial protocol, informed consent form etc.) and the date of the review should be clearly stated on the written EC approval/favorable opinion.

During the study, any amendment or modification to the protocol must be submitted to the EC before implementation, unless the change is necessary to eliminate an immediate hazard to the patients, in which case the EC should be informed as soon as possible. The EC should also be informed of any event likely to affect the safety of patients or the continued conduct of the clinical trial. All safety updates will be sent to the EC.

A progress report shall be sent to the EC at least annually and a summary of the clinical trial's outcome at the end of the clinical trial.

15 STUDY MONITORING

15.1 RESPONSIBILITIES OF THE INVESTIGATOR

The Investigator is required to ensure compliance with all procedures required by the clinical trial protocol. The Investigator agrees to provide reliable data and all information requested by the protocol and to ensure Sponsor representatives direct access to source documents.

The confidentiality of the patient's data shall be protected at all times.

The Investigator may appoint other individuals as Sub-investigators to assist in the conduct of the clinical trial. All Sub-investigators shall be listed and shall work under the responsibility of the Investigator. All Sub-investigators shall be provided with a copy of the protocol and trained.

15.2 RESPONSIBILITIES OF THE SPONSOR

The Sponsor is responsible to regulatory authorities for taking all reasonable steps to ensure the proper conduct of the clinical trial as regards ethics, protocol compliance, and integrity and validity of data. The site will be contacted at regular intervals by a representative of the monitoring team to review study progress, Investigator and patient compliance with clinical trial protocol requirements and any emergent issues. Monitoring contacts will include a review of patient informed consent, patient recruitment and follow-up, AE documentation, product allocation, product accountability and data quality.

15.3 SOURCE DOCUMENT REQUIREMENTS

In accordance with ICH-GCP, the monitoring team shall check eCRF entries against source documents, except for the pre-identified source data directly recorded in the CRF. The informed consent form will include a statement by which the patient allows the Sponsor's duly authorized personnel, the Ethics Committee and the regulatory authorities to have direct access to original medical records that support CRF data. These personnel shall maintain the confidentiality of all

personal identity and personal medical information (according to confidentiality and personal data protection norms).

16 ADDITIONAL REQUIREMENTS

16.1 CURRICULUM VITAE

A current copy of the curriculum vitae describing the experience, qualification and training of the Investigator and Sub-investigator shall be signed, dated and provided to the Sponsor prior to the beginning of the clinical trial.

16.2 RECORD RETENTION IN STUDY SITES

The Investigator shall maintain the confidentiality of all study documentation, and take measures to prevent accidental or premature destruction of these documents.

The Investigator shall retain the study documents at least 15 years after the completion or discontinuation of the clinical trial, or longer should this be required by regulatory requirements.

Should archiving no longer be ensured by the Investigator, he or she shall inform the Sponsor and the relevant records will be transferred to a mutually agreed upon designee.

16.3 CONFIDENTIALITY

All information disclosed or provided by the Sponsor (or any company/institution acting on their behalf), or produced during the clinical trial, including, but not limited to, the clinical trial protocol, personal data relating to the patients, CRFs and the results obtained during the course of the clinical trial, is confidential, prior to the publication of results. The Investigator and any person under his/her authority agree to not disclose any information to any third party without the Sponsor’s written prior approval.

16.4 PROPERTY RIGHTS

All information, documents and product provided by the Sponsor or its designee are and remain the sole property of the Sponsor.

All the results, data, documents and inventions that arise directly or indirectly from the clinical trial in any form shall be the immediate and exclusive property of the Sponsor.

16.5 DATA PROTECTION

The patient's personal data shall be processed in compliance with all applicable laws and regulations.

The Sponsor shall take all appropriate measures to safeguard and prevent access to personal data pertaining to the Investigator and/or to the patients by any unauthorized third party.

16.6 INSURANCE COMPENSATION

The Sponsor certifies that it has taken out a liability insurance policy covering all clinical trials under its sponsorship. This insurance policy is in accordance with local laws and requirements. The insurance of the Sponsor does not relieve the Investigator and the collaborators from any obligation to maintain their own liability insurance policy. An insurance certificate will be provided to the EC or regulatory authorities.

16.7 SPONSOR AUDITS AND INSPECTIONS BY REGULATORY AGENCIES

The Investigator shall permit auditing by or on the behalf of the Sponsor and inspection by regulatory authorities. The Investigator agrees to allow the auditors/inspectors to have direct access to study records for review, being understood that these are bound by professional secrecy, and as such will not disclose any personal identity or personal medical information. The Investigator will make every effort to assist with the audits and inspections by providing access to all facilities, data, and documents.

As soon as the Investigator is notified of a planned inspection by the authorities, he or she shall inform the Sponsor and authorize the Sponsor to participate in this inspection. Any result and information arising from the inspections by the regulatory authorities shall be immediately communicated to the Sponsor.

The Investigator shall provide appropriate corrective actions for all issues detected during the audit or inspections.

16.8 PREMATURE DISCONTINUATION OF THE STUDY OR PREMATURE CLOSE-OUT OF A SITE

The Sponsor has the right to terminate the study at any time, for any reason.

The Investigator may terminate participation upon thirty (30) days prior written notice if the study site or the Investigator for any reason becomes unable to perform or complete the clinical trial.

In the event of premature discontinuation of the study, for any reason whatsoever, the EC and regulatory authorities must be informed according to applicable regulatory requirements.

16.9 PUBLICATIONS AND COMMUNICATIONS

The results of this study may be published or presented at scientific meetings. Should this be foreseen, the investigator agrees to submit all manuscripts or abstracts to the Sponsor prior to submission. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

17 CLINICAL TRIAL PROTOCOL AMENDMENTS

Any change or addition to the protocol can be made only through a written protocol amendment that must be approved by the Sponsor, Health Authorities where required, and the EC. Only amendments that are required for patient safety may be implemented prior to EC approval. Despite the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient even if this represents a deviation from the protocol.

18 BIBLIOGRAPHIC REFERENCES

1. De Groot, H, Brand PLP, Fokkens WF et al. Allergic rhinoconjunctivitis in children. BMJ. 2007 Nov 10; 335(7627): 985–988.
2. Hakansson K, Thomsen SF, Ulrik CS, Porsbjerg C, Backer V. Increase in the prevalence of rhinitis among Danish children from 1986 to 2001. Pediatr Allergy Immunol 2007;18:154-9.
3. ADVANCES in orthomolecular research - Volume 3 Issue 5 Perilla: An Allergy Fighting Herb.
4. Shin TY, Kim SH, Kim SH, et al. Inhibitory effect of mast cell-mediated immediate-type allergic reactions in rats by Perilla frutescens. Immunopharmacol Immunotoxicol. 2000 Aug;22(3):489-500.
5. Imaoka K, Inouye S, Takahashi et al. Effects of Perilla frutescens extract on anti-DNP IgE antibody production in mice. Arerugi. 1993 Jan;42(1):74-80.
6. Ueda H, Yamazaki C, Yamazaki M. Luteolin as an anti-inflammatory and anti-allergic constituent of Perilla frutescens. . Biol Pharm Bull. 2002 Sep;25(9):1197-202
7. Makino T, Furuta Y, Wakushima H et al. Anti-allergic effect of Perilla frutescens and its active constituents. Phytother Res. 2003 Mar;17(3):240-3.
8. Shaik YB, Castellani ML, Perrella A et al. Role of quercetin (a natural herbal compound) in allergy and inflammation.J Biol Regul Homeost Agents. 2006 Jul-Dec;20(3-4):47-52.
9. Muehleisen B, Gallo RL J. Vitamin D in allergic disease: shedding light on a complex problem Allergy Clin Immunol. 2013 Feb;131(2):324-9.
10. Bozzetto S, Carraro S, Giordano G et al. Asthma, allergy and respiratory infections: the vitamin D hypothesis. Allergy. 2012 Jan;67(1):10-7.
11. Ariano R. Efficacy of a novel food supplement in the relief of the signs and symptoms of seasonal allergic rhinitis and in the reduction of the consumption of anti-allergic drugs. Acta Biomed. 2015 Apr 27;86(1):53-8.
12. Cohen J, Statistical Power Analysis for the Behavioral Sciences, 1969.
13. Ka-Kit Mak et Al., Pediatrics and Neonatology (2013) 54, 239-245