# LLB-2016-01

# Statistical Analysis Plan

| | |
|---|---|
| **Title:** | Randomized, double-blind, placebo-controlled study to measure 2L®ALERG efficacy on symptoms of allergic rhinitis and allergic rhinoconjunctivitis in patients with a seasonal allergy to grass pollen. |
| **EUDRA CT number:** | 2016-000097-38 |
| **ClinicalTrials.gov number** | NCT02690935 |
| **Date:** | 29 February 2016 |
| **Coordinating author:** | Jacques BRUHWYLER, PhD,<br>Director of Biostatistics<br>ECSOR SA/NV |

**Approved by:**

| | | | |
|---|---|---|---|
| **Medical Advisor** | Dr. Xavier VAN DER BREMPT | | |
| | Name | Signature | Date |
| **Principal Investigator** | Dr. Stéphane HEIJMANS | | |
| | Name | Signature | Date |
| **Sponsor's Project Manager** | Béatrice LEJEUNE | | |
| | Name | Signature | Date |
| **CRO Director of Biostatistics** | Jacques BRUHWYLER | | |
| | Name | Signature | Date |

## TABLE OF CONTENTS

**PAGE**

## LIST OF FIGURES

**PAGE**



## LIST OF TABLES

**PAGE**

# LIST OF ABBREVIATIONS

| | |
|---|---|
| AE | Adverse Event |
| AUC | Area Under the Curve |
| CRF | Case Report Form |
| CRO | Clinical Research Organization |
| CSR | Clinical Study Report |
| ICF | Inform Consent Form |
| ICH | International Conference on Harmonization |
| IgE | Immunoglobulin E |
| IL | Interleukin |
| ITT | Intention-To-Treat |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MS | Medication Score |
| PP | Per Protocol |
| QoL | Quality of Life |
| RM | Rescue mediation |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SAR | Serious Adverse Reaction |
| SmPC | Summary of Product Characteristics |
| SUSAR | Suspected Unexpected Serious Adverse Reaction |
| T5 SS | Total 5 Symptoms Score |

# 1. INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to describe:

- The study features as per protocol (dated 22 December 2015) in terms of objectives, study design and study conduct.
- The endpoints, the study cohorts, the study variables and the derived data.
- The planned statistical analyses and methodologies.
- The tables, figures and listings

# 2. STUDY OBJECTIVES

The primary objective of the study is to demonstrate the superiority of 2L®ALERG over placebo in terms of efficacy on the symptoms of allergic rhinitis and allergic rhinoconjunctivitis in patients with seasonal allergy to grass pollen, corrected according to rescue medication intake.

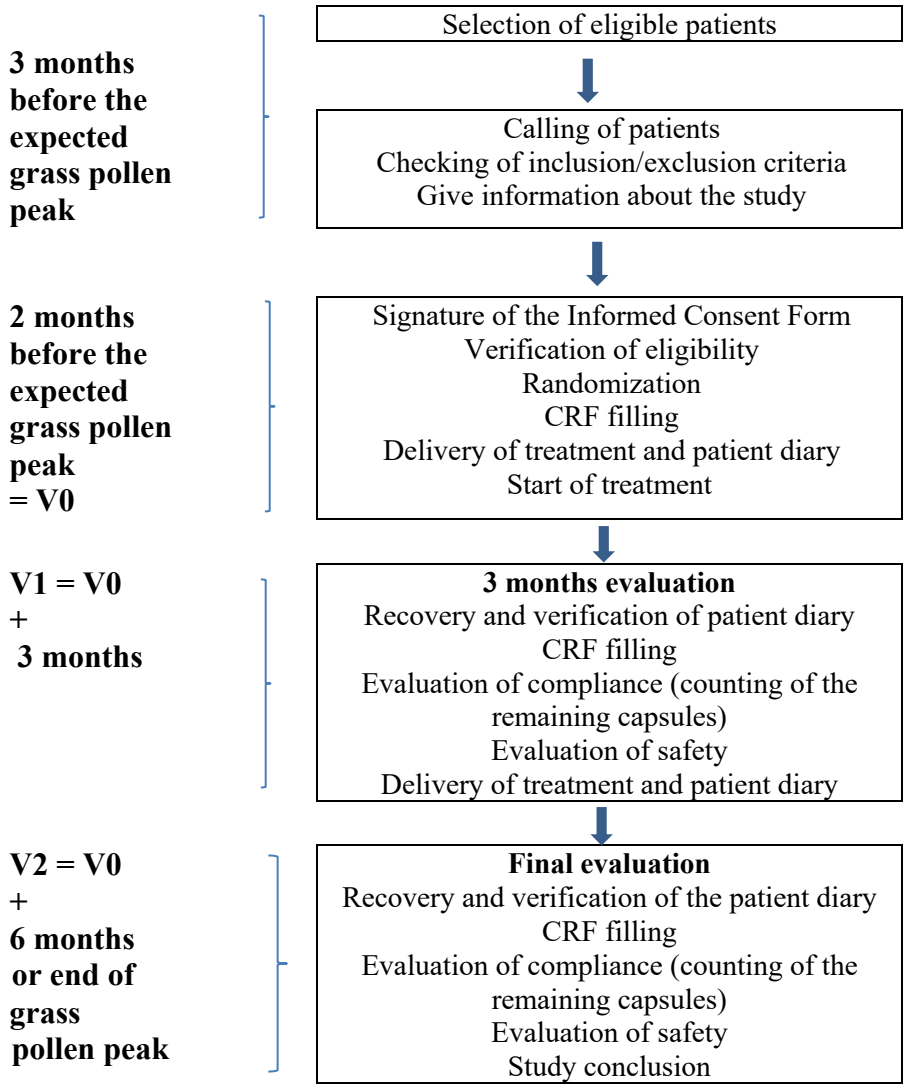
The secondary objectives of the study are:

- To compare the allergy symptoms in patients treated with 2L®ALERG or with a placebo.
- To compare the rescue medication intake in patients treated with 2L®ALERG or with a placebo.
- To compare the quality of life (QoL) in patients treated with 2L®ALERG or with a placebo.
- To compare the safety in patients treated with 2L®ALERG or with a placebo.

# 3. STUDY DESIGN OVERVIEW

The study flow chart can be found in Figure 1.

**Figure 1 Study flow chart**




- Experimental design: Double-blind, parallel-group, randomised, multicentre, interventional, placebo-controlled study.
- Treatment allocation: Balanced allocation between 2L®ALERG and placebo (1:1).
- Blinding: double-blind study. The investigator and the patient are blinded.
- The study will last maximum 9 months: duration of inclusion = 1 month and patient's follow up = 6-8 months.
- The duration of 2L®ALERG exposure will be 6 months.

- Data collection: Paper Case Report Form (CRF).
- Number of investigational centres = 20.
- Number of patients/centre = 5
- Total number of patients to be enrolled = 100.
- Expected number of completed patients = 80.
- Treatment group: 1 capsule of 2L®ALERG daily (fasting in the morning), following the numerical order of 1 to 10 capsules, for approximately 6 months.
- Control group: Placebo: 1 capsule of Placebo daily (fasting in the morning), following the numerical order of 1 to 10 capsules, for approximately 6 months.

# 4. CONDUCT OF STUDY

## 4.1. Study procedures

The study procedures are summarised Table 1.

**Table 1 Summary of study procedures**

| | **Screening (– 1 month)** | **V0 (2 months before grass pollen peak)** | **V1 (3 months after V0)** | **V2 (6 months after V0 or end of grass pollen peak)** |
|---|---|---|---|---|
| Selection of patients<br>Verification of inclusion/exclusion criteria<br>Performance of allergy tests if needed | ● | | | |
| Give information about the study<br>Give the Inform Consent Form to the patient | ● | | | |
| Eligibility check | | ● | | |
| Signature of the Informed Consent Form | | ● | | |
| Randomization | | ● | | |
| Demography | | ● | | |
| Medical history | | ● | | |
| Physical examination | | ● | ○ | ○ |
| Allergy treatment history | | ● | | |
| Delivery of treatment for 3 months | | ● | ● | |
| Distribution of the patient diary | | ● | ● | |
| Start of treatment | | ● | | |
| Diary card filling by the patient | | ● | ● | ● |
| Patient diary card control | | | ● | ● |
| Compliance control | | | ● | ● |
| Relevant (allergy-related) concomitant medications (except rescue medications) | | ● | ● | ● |
| Safety control (AE/SAE) | | | ● | ● |
| Study conclusion | | | | ● |

● Compulsory
○ Optional

- The following demographic data will be collected during the first visit: date of birth, gender, ethnic group, weight, height, smoking habits and alcohol use status.
- Medical history, treatment history, concomitant treatments and patient's physical examination will also be documented during V0.

- The allergy must be confirmed by positive skin test and/or the presence of IgE for grasses (prick test defined as positive if higher than or equal to half the negative control; IgE are positive if at least class 3 (≥ 3.5 kU / L); these tests must have been made at the latest during the first visit.
- A patient diary will be given to each patient:
  - For the evaluation of the total 5 symptoms score T5SS. The patients will note their symptoms intensity every day (sneezing, rhinorrhoea, nasal pruritus, itching and/or eye tearing and nasal obstruction).
  - For recording daily rescue medications. The patients will note the type of compound taken and the posology on a day to day basis.
  - The patient will take note every day of his/her QoL by filling in three questions included in his/her diary card: Did you sleep well? – Can you work normally? – How do you feel?
  - The patient will take note of the date of the treatment start and the date of onset of symptoms.
- This patient diary will be given to the patient at each visit, and will be brought back at the next visit, it will be reviewed and validated by the investigator and will be part of the CRF.
- All relevant (related to allergy) concomitant medications (except rescue medications, which are part the diary card) taken by the patient and communicated to the investigator at the time of the visit will be recorded in the appropriate section of the CRF.
- The AEs and SAEs will be recorded at V1 and V2 in order to assess safety.

## 4.2. Rescue and concomitant medications

The **allowed treatments** are the treatments already established for associated pathologies not liable to have an impact on the proper conduct of the study.

The **rescue medications allowed** in the first-line adjuvant treatment are:

- Oral or topical antihistamines (nasal or eye)
- Eye cromoglycate
- Topical nasal corticosteroids (in case of failure or insufficiency of those above).

The **not allowed treatments** are:

- Oral or injectable corticosteroids
- Anti-leukotrienes

## 4.3. Monitoring of compliance

The investigator will ask the patient to bring back drug boxes (full and empty blisters) at each visit.

The counting of the remaining capsules will be made by the investigator.

In case the patient would come in consultation a few days before the end of the treatment period, the patient will be allowed to keep the blister to complete the sequence.

A global compliance will be calculated for each patient on the total duration of treatment. Global compliance will be acceptable if it is between 80% and 120%. If values <80% or >120%, the patient will be eliminated from the analysis according to the protocol (PP) and will be taken into account in the analysis by intention to treat (ITT).

## 4.4. Rules for study discontinuation and completion

The criteria for premature discontinuation of the study are:

- Withdrawal of consent,
- Protocol violation,
- Intolerance to treatment,
- Voluntary discontinuation of treatment,
- Intake of a forbidden treatment during the study,
- Proved pregnancy,
- Decision at the discretion of the investigator.

The study will be considered terminated at the end of the participation of the last patient entered into the study, and when all collected data needed for evaluation have been verified and validated.

## 4.5. Adverse events

### 4.5.1. Definitions

An adverse event is defined as any untoward medical occurrence in a patient or a participant in a clinical trial, whether or not considered drug related.

All adverse events encountered during the study, which are observed by the physician or patient-reported, will be recorded in the CRF in the section provided for this purpose.

The intensity of adverse events will be quoted as follows:

- 1 = mild
- 2 = moderate

- 3 = severe

For each adverse event, the investigator will have to rule on the causal relationship to the medical product on the following scale: none, possible, probable or certain.

An AE is considered as a Serious Adverse Event (SAE) when it:

- Results in death,
- Involves life-threatening,
- Results in incapacity or temporary or permanent disability,
- Requires or prolongs patient hospitalization,
- Causes congenital anomaly or neonatal
- Is medically significant (requires care to avoid worsening)

Serious Adverse Reaction (SAR): A SAR is a SAE considered related to the investigational study product.

An expected adverse event is an event mentioned in the most recent version of the Summary of Product Characteristics (SmPC) for drugs already having a marketing authorization.

The expected effects or serious adverse events will be subject to a delayed declaration by the sponsor to the competent authorities.

Unexpected Serious Adverse Reactions (SUSARs) are events where the nature, severity, frequency or developments are not consistent with product information, with practiced acts and with methods used during the study, as defined in the SmPC. Unexpected serious adverse events will be subject to a statement within 7 days after their knowledge by the sponsor to the competent authorities.

### 4.5.2. Safety endpoints

Collecting data and analysis of safety endpoints described above will be performed by spontaneous statement or during monitoring.

A SAE report form will be attached to the CRF (collecting symptoms, dates, evolution, judgment of causality by the physician, actions taken)

All AEs / SAEs / SARs / SUSARs will be subject to coding in terms of System Organ Class and Preferred Terms, using the latest version of the dictionary MedDRA (Medical Dictionary for Regulatory Activities).

### 4.5.3. List of expected AEs

In the framework of this study, expected AEs are those mentioned in the SPC:

- In exceptional cases, it may appear dyspepsia when taken fasted (in this case, the granules will be taken one hour after the meal)
- Difficulties in falling asleep can occur if taken after 16 hours
- As with all homeopathic treatment, print of worsening symptoms can occur, that usually disappears after a few days.

### 4.5.4. Management of adverse events

All SAEs require filling a SAE report, whether expected or not expected. The investigator must ensure that the information entered on this report is accurate and clear.

SAE should be reported immediately to the sponsor (within 24 hours of being highlighted by the investigator).

After being scanned, the SAE report can be sent by e-mail to the following person in charge of pharmacovigilance:

**Dr. Paul Willems**
**Semaphar sprl**
**31, Rue Francourt**
**1370 Lathuy (Jodoigne)**
**Belgium**
**Mobile: 0477/60.72.72**
**E-mail address: pwillems.md@icloud.com**

The person in charge of pharmacovigilance will have a copy of the randomization list available in case unblinding is unavoidable after his/her discussion with the investigator.

After receipt of notification of a SUSAR, the sponsor shall declare to the regulatory authorities. Once a year, the sponsor will prepare an annual safety report.

### 4.5.5. Modalities and duration of follow up after the occurrence of adverse events

Given the nature of the study treatment, the follow-up shall be two months after the end of the study.

## 4.6. Sample size justification

The objective of the study will be to show the superiority of 2L®ALERG over placebo in the treatment of patients suffering from seasonal allergy to grass pollen.

For the sample size calculations two references have been used. The first is a study conducted with 2®LALERG versus placebo in patients with a pollen allergy [1].

The second is a more theoretical publication from Clark and Schall (2007) supporting the recommendations made in a World Allergy Organization document on methodological aspects of immunotherapy trials. The average of the Average Rhinoconjunctivitis Total Symptom Score (ARTSS) and Average Rescue Medication Score (ARMS) should be considered as a primary efficacy variable in clinical trials of immunotherapy for allergic rhinoconjunctivitis [2].

The global score calculated in the paper of Van der Brempt et al. (2011) [1], taking into account the T5SS total score and the RMS total score, fits very well with the recommendation from Clark and Schall (2007) [2].

The Figure 5 of Van der Brempt et al.'s paper has been used to evaluate the area under the curve (AUC) of global score for the placebo and 2L®ALERG groups [1].

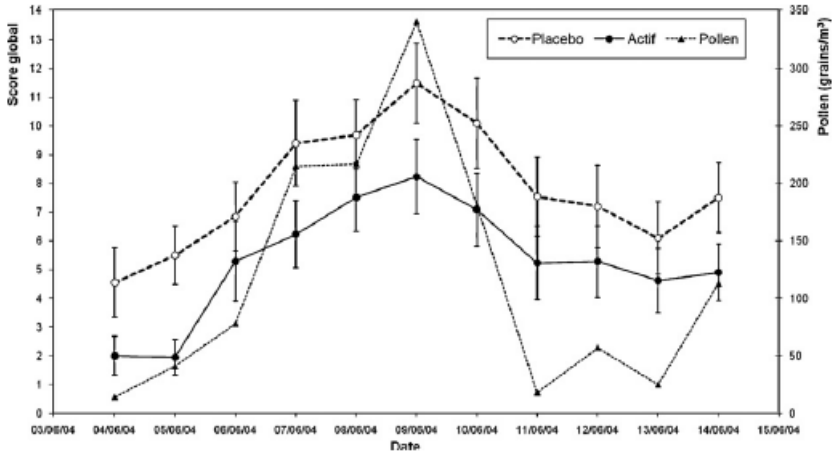



Fig. 5. Comptages polliniques et évolution du score global (moyenne et écart-type) dans les groupes actif et placebo pendant la période d'étude.

The values were approximately 80 for the placebo group and 55 for the treated group (a reduction of about 30% with the active treatment. These values have been used to build several sample size scenarios.

**Table 2 Sample size calculation**

| Scenario | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|
| **Test significance level, $\alpha$** | 0.050 | 0.050 | 0.050 | 0.050 | 0.050 |
| **1 or 2 sided test?** | 2 | 2 | 2 | 2 | 2 |
| **Group Placebo mean, $\mu_1$** | 80.000 | 80.000 | 80.000 | 80.000 | 80.000 |
| **Group 2L®ALERG mean, $\mu_2$** | 55.000 | 55.000 | 55.000 | 55.000 | 55.000 |
| **Difference in means, $\mu_1 - \mu_2$** | 25.000 | 25.000 | 25.000 | 25.000 | 25.000 |
| **Common standard deviation, $\sigma$** | 20.000 | 25.000 | 30.000 | 35.000 | 40.000 |
| **Effect size, $\delta = \lvert\mu_1 - \mu_2\rvert / \sigma$** | 1.250 | 1.000 | 0.833 | 0.714 | 0.625 |
| **Power ( % )** | 90 | 90 | 90 | 90 | 90 |
| **n per group** | 15 | 23 | 32 | 43 | 55 |
| **Total N completed patients** | 30 | 46 | 64 | 86 | 110 |

A sample size of 32 patients in each group will have 90% power to detect a difference in means of 25 (the difference between a placebo group mean, $\mu_1$, of 80 and a 2L®ALERG group mean, $\mu_2$, of 55) assuming that the common standard deviation is 30 using a two group t-test with a 0.05 two-sided significance level.
With a sample size of 43 patients in each group, the same assumptions are valid with a common standard deviation of 35.
The final recommendation will be to include 50 patients per group in order to achieve at least 40 evaluable patients per group taking into account a potential drop-out rate of 20%.

## 4.7. Interim analysis

No interim analysis is planned.

# 5. DATA EVALUATION: CRITERIA FOR EVALUATION OF OBJECTIVES

## 5.1. Study cohorts

### 5.1.1. Total cohort

The total cohort will include all screened patients having signed the informed consent.

### 5.1.2. Intention to treat cohort

The primary cohort for the efficacy and safety assessments will be the ITT population. It will include patients having been randomised and for whom at least one measure is available after the intake of at least one dose of the study drug.

### 5.1.3. Per protocol cohort

The secondary cohort for the efficacy and safety assessments will be the PP population. It will include patients having completed the study, who did not deviate from the protocol and in whom compliance was in a range between 80% and 120% during the whole treatment period.

## 5.2. Study variables, derived and transformed data

### 5.2.1. Screening, demography and baseline characteristics

#### 5.2.1.1. Study variables

- Visit 0 date: date variable
- Written informed consent date: date variable
- Inclusion criteria: binary discrete variable: no/yes
- Exclusion criteria: binary discrete variable: no/yes
- Gender: discrete nominal variable: female/male
- Birth date: date variable
- Height (cm): continuous variable
- Weight (kg): continuous variable
- Blood pressure:
  - Systolic blood pressure (mmHg): continuous variable
  - Diastolic blood pressure (mmHg): continuous variable

- Heart rate (beat/min): continuous variable
- Smoking status: discrete nominal variable
  - Non-smoker
  - Previous smoker
  - Smoker
- Number of cigarettes/pipes/cigars (nb/day): continuous variable
- Alcohol: discrete nominal variable
  - <1 glass/day
  - ≥1 glass/day
- Number of alcohol glasses/day: continuous variable
- Ethnic origin: discrete nominal variable
  - Caucasian
  - Black
  - Asian
  - Other + specification (text variable)
- Allergy diagnosed since (year): partial date variable
- Allergy diagnosed today: binary discrete variable: no/yes
- Allergy confirmed by positive prick-test: binary discrete variable: no/yes
- Date of confirmed diagnosis by prick-test: date variable
- Allergy confirmed by presence of IgE for grasses: binary discrete variable: no/yes
- Date of confirmed diagnosis by presence of IgE: date variable
- Allergy treatment history during the two last pollen seasons:
  - Name of medication: text variable
  - Dose of medication: text variable
  - Units of dose: text variable
  - Regimen: text variable
  - Year: partial date variable
- Physical examination: eight body systems + other: discrete binary variables
  - Normal
  - Abnormal
  - Description: text variable

#### 5.2.1.2. Derived variables

- Age (year) = TRUNC [(Visit 0 date - Birth date) / (60 x 60 x 24 x 365.25)][1]
- Body Mass Index (BMI) (kg/m²) = Weight / (Height/100)²
- Allergy duration (year) = TRUNC [(Visit 0 date - Date of allergy diagnosis) / (60 x 60 x 24 x 365.25)]
- Time since confirmation of grass pollen allergy (year) = TRUNC [(Visit 0 date - Date of prick-test or presence of IgE confirmation) / (60 x 60 x 24 x 365.25)]

### 5.2.2. Efficacy parameters

#### 5.2.2.1. Study variables

- Treatment start date: date variable
- Allergy symptoms start date: date variable
- Diary dates: date variables
- T5SS (each day) (sneezing, rhinorrhoea, nasal pruritus, eye itching and tearing, and nasal obstruction) intensity: discrete ordinal variable: none, mild, moderate, severe
- Rescue medication name: text variable
- Rescue medication dose: text variable
- Quality of life questions: discrete ordinal variable
  - Did you sleep well?: 4 levels
  - Can you work normally?: 4 levels
  - How do you feel?: 4 levels

#### 5.2.2.2. Derived variables

- Time between treatment and allergy start dates (day) = (allergy symptoms start date – treatment start date) / (60 x 60 x 24)
- Daily quality of life score = ∑ of three question scores
- Daily total T5SS score = ∑ of T5SS individual scores
- Daily total T5SS score corrected for rescue medications = (∑ of T5SS individual scores)
  - + 2 (for oral antihistamine drugs)
  - +1 for local treatment (nasal or eye)
  - +1 for ocular cromoglycate

[1] The software IBM-SPSS Statistics calculates the difference between two dates in seconds.

  - +1 for nasal topical corticosteroids

### 5.2.3. Safety parameters

#### 5.2.3.1. Study variables

- Dates of Visit 1 and Visit 2: date variables
- Physical examination (optional at Visits 1 and 2): eight body systems + other: discrete binary variables
  - Normal
  - Abnormal
  - Description: text variable
- Vital signs (optional at Visits 1 and 2):
  - Systolic blood pressure (mmHg): continuous variable
  - Diastolic blood pressure (mmHg): continuous variable
  - Heart rate (beat/min): continuous variable
- Total number of remaining capsules at Visit 1: continuous variable
- Total number of remaining capsules at Visit 2: continuous variable
- AEs: description (text variable), intensity (ordinal variable), start date and end date (date variables), ongoing (binary variable: yes/no), action taken, outcome and relationship to study medication (nominal variables)
- SAEs: full description narrative.
- Concomitant medications: medication trade name, dose, units, regimen (text variables), start date, stop date (date variables) or ongoing (binary discrete variable: yes/no).

#### 5.2.3.2. Derived variables

- Coding MedDRA (System Organ Class) of each AE/SAE: numeric code
- Coding MedDRA (System Organ Class) of each AE/SAE: text variable
- Coding MedDRA (Preferred Term) of each AE/SAE: numeric code
- Coding MedDRA (Preferred Term) of each AE/SAE: text variable

### 5.2.4. Study conclusion

#### 5.2.4.1. Study variables

- Completion of the study: binary discrete variable: no/yes
- If no, date of premature discontinuation: date variable.

- If no, drop-out category: discrete nominal variable: SAE, non-serious AE, protocol violation, consent withdrawal, moved from study area, lost to follow-up but alive (+date the patient was known to be alive), death (+ date of death) and other + specifications (text variables).
- Investigator' signature: binary discrete variable: no/yes + date variable

#### 5.2.4.2. Derived variable

- Total duration of the study (day) = (Visit 2 date or Premature discontinuation date – Visit 0 date) / (60 x 60 x 24)
- Total number of remaining capsules = Number of remaining capsules at Visit 1 + Number of remaining capsules at Visit 2
- Compliance (%) = ([Number of capsules provided to the patient – Total number of remaining capsules] / Total duration of the study) x 100

### 5.2.5. Other variables

#### 5.2.5.1. Study variables[2]

- Date of grass pollen season start = date variable
- Date of the grass pollen peak = date variable
- Date of grass pollen season end = date variable

#### 5.2.5.2. Derived variable

- Time between treatment start and pollen season start (day) = (Date of grass pollen season start – Date of treatment start) / (60 x 60 x 24)
- Time between treatment start and pollen peak (day) = (Date of grass pollen peak – Date of treatment start) / (60 x 60 x 24)
- Time between treatment start and pollen season end (day) = (Date of grass pollen season end – Date of treatment start) / (60 x 60 x 24)

[2] These dates will be communicated by the sponsor on the basis of official epidemiological data in Belgium.

# 6. STATISTICAL METHODOLOGIES

## 6.1. General principles

- IBM SPSS Statistics (Version 21.0 and eventual updates/upgrades) and StatXact (Version 6.0) will be used for the statistical analyses.
- Missing values will not be replaced nor extrapolated.
- The primary cohort for the efficacy and safety analyses will be the ITT cohort.
- The secondary cohort for the efficacy and safety analyses will be the PP cohort.
- All statistical analyses will be replicated in the PP cohort, only if it differs by more than 10% of the ITT cohort in terms of number of patients.
- The primary endpoint being unique and no interim analysis being planned, no correction will be applied for multiplicity. A p value lower than 0.05 will be considered statistically significant.
- No correction for multiplicity being applied for the numerous secondary endpoints, p values lower than 0.05 will be considered with caution, as potentially indicative of possible statistically significant differences.
- The number of observations being largely superior to 30, the central limit theorem will be invoked and all parametric tests will be allowed without verification of normality.
- Changes to the planned analyses of the protocol and/or to the planned analyses from the SAP will be documented in the Statistical Report and in the Clinical Study Report (CSR).

## 6.2. Subject eligibility and attrition from the study

A flow diagram based on the CONSORT template will be drawn with:

- Number of patients enrolled (Total cohort)
- Number and % of screen failures and reason for exclusion
- Number and % of patients randomised in the two treatment groups (ITT cohort)
- Number and % of patients dropping out before Visit 2 and reason for dropping out
- Number and % of patients completing Visit 2 in the two treatment groups
- Number and % of patients completed per protocol (PP cohort) in the two treatment groups

## 6.3. Demographic and baseline characteristics

Descriptive statistics will be used to characterize the population at baseline:

- Continuous variables will be characterised by the N, n with missing data, mean, standard deviation (SD), median, minimum and maximum.
- Discrete variables will be characterised by the N, n for each category, n with missing data and corresponding percentages.

## 6.4. Balance between the two groups at baseline

At baseline, the balance between the two treatment groups will be assessed using:

- Independent Student's t tests for continuous variables.
- Chi-square tests, Fisher's exact tests or Mann-Whitney's tests, as appropriate, for discrete variables

## 6.5. Efficacy analysis

### 6.5.1. Analysis of the primary efficacy endpoint

The primary endpoint will be the area under the curve (AUC) of the overall score established according to the total 5 symptoms score (T5SS) and medication score (MS) according to time from the start of treatment until the end of the patient follow-up.
The five symptoms (sneezing, rhinorrhoea, nasal pruritus, eye itching and tearing, and nasal obstruction) will be assessed daily by patients on a scale from 0 (no symptoms) to 3 (severe symptoms) giving a total score ranging from 0 to15.
The rescue medications (RM) allowed in the first-line adjuvant treatment will be codified to establish a score.
The allowed RM are the oral antihistamines (two points per day of use) or local treatment (nasal or eye; a point per day), and the ocular cromoglycate (one point per day).
In case of failure or in case of insufficiency of rescue medications mentioned above, the nasal topical corticosteroids (one point per day of use) will be allowed.

The AUC will be compared between the treated and the placebo group using an Independent Student's t test.

### 6.5.2. Analyses of the secondary efficacy endpoints

The secondary efficacy endpoints will be:

- The primary endpoint re-analysed around the grass pollen peak: AUC calculated from one week before the official pollen peak up to the end of the grass pollen season (continuous variable).
- The total 5 symptoms score (T5SS) at the pollen peak (continuous variable)
- The individual scores of the 5 symptoms at the pollen peak (discrete variables)
- The consumption of rescue medications score at the pollen peak (discrete variable)

- The evaluation of the QoL: AUC (total score of 3 questions of QoL included in the diary card on the Y-axis, and time on X axis) during the entire follow-up period (continuous variable).
- The evaluation of the QoL: AUC (total score of 3 questions of QoL included in the diary card on the Y-axis, and time on X axis) from one week before the grass pollen peak up to the end of the grass pollen season (continuous variable).

Continuous variables will be compared between the treated and the placebo groups using Independent Student's t tests.

Discrete variables will be compared between the treated and the placebo groups using Mann-Whitney's tests.

## 6.6. Safety analysis

- The frequency of AEs and SAEs will be compared between the two groups using chi-square tests or Fisher's exact tests, as appropriate.
- The same analysis will be replicated for AEs and SAEs considered as possibly, probably or definitely related to the study medication.
- Comparative tables with AEs and SAEs (overall and related only) classified according to MedDRA SOCs and PTs, and treatment groups will be provided.
- Narratives will be provided for each SAE.
- Relevant concomitant medications will be presented descriptively in listings by patient and treatment group.

## 6.7. Other variables

- The overall treatment duration will be compared between the two groups using an Independent Student's t test.
- Compliance will be compared between the two groups using an independent Student's t test.

# 7. TABLES, FIGURES AND LISTINGS

## 7.1. Tables

### 7.1.1. Descriptive analyses

Classical descriptive tables (such as Table 3 and Table 4) will be produced.

**Table 3 Template of a descriptive table for continuous variables**

| | N | | Mean | Median | SD | Min | Max |
|---|---|---|---|---|---|---|---|
| | Valid | Missing | | | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |

**Table 4 Template of a descriptive table for discrete variables**

| | | N | Percent | Valid Percent | Cumulative Percent |
|---|---|---|---|---|---|
| Valid | | | | | |
| | | | | | |
| | | | | | |
| Missing | | | | | |
| Total | | | | | |

### 7.1.2. Inferential analyses

Classical inferential tables (such as Table 5 and Table 6) will be produced.

**Table 5 Template of an inferential table for continuous variables to compare the different strata or subgroups**

| | Treatment | N | Mean | Std. Deviation | Std. Error Mean |
|---|---|---|---|---|---|
| **Variable 1** | **Treatment 1** | | | | |
| | **Treatment 2** | | | | |
| **Variable 2** | **Treatment 1** | | | | |
| | **Treatment 2** | | | | |
| **Variable 3** | **Treatment 1** | | | | |
| | **Treatment 2** | | | | |
| **Variable 4** | **Treatment 1** | | | | |
| | **Treatment 2** | | | | |
| **Variable 5** | **Treatment 1** | | | | |
| | **Treatment 2** | | | | |

**Table 6 Template of an inferential table for discrete variables to compare the different strata or subgroups**

| | | | Treatment | | Total |
|---|---|---|---|---|---|
| | | | 1 | 2 | |
| **Variable 1** | **Value 1** | **Count** | | | |
| | | **% within subgroup** | | | |
| | **Value 2** | **Count** | | | |
| | | **% within Treatment** | | | |
| | **Value 3** | **Count** | | | |
| | | **% within Treatment** | | | |
| **Total** | | **Count** | | | |
| | | **% within Treatment** | ***100.0%*** | ***100.0%*** | ***100.0%*** |

## 7.2. Figures

The following figure templates will be used to illustrate the results of the study:

**Figure 2 Over-time modification of grass pollen levels and T5SS (mean ± standard deviation) in the active and placebo groups during the whole study period**

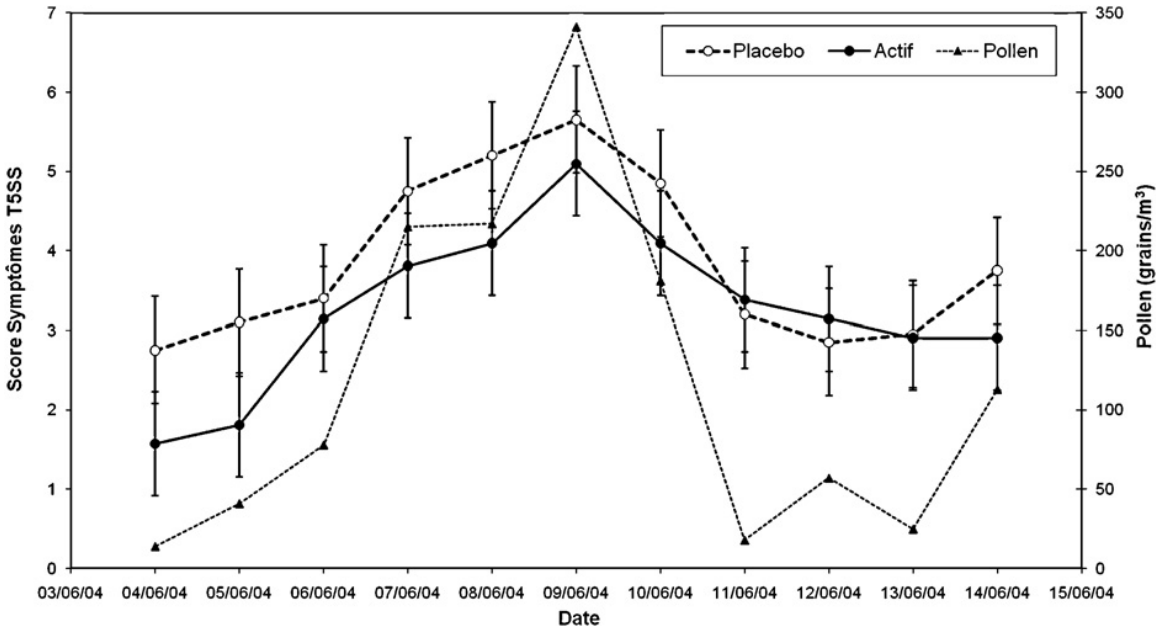



**Figure 3 Over-time modification of grass pollen levels and RM score (mean ± standard deviation) in the active and placebo groups during the whole study period**

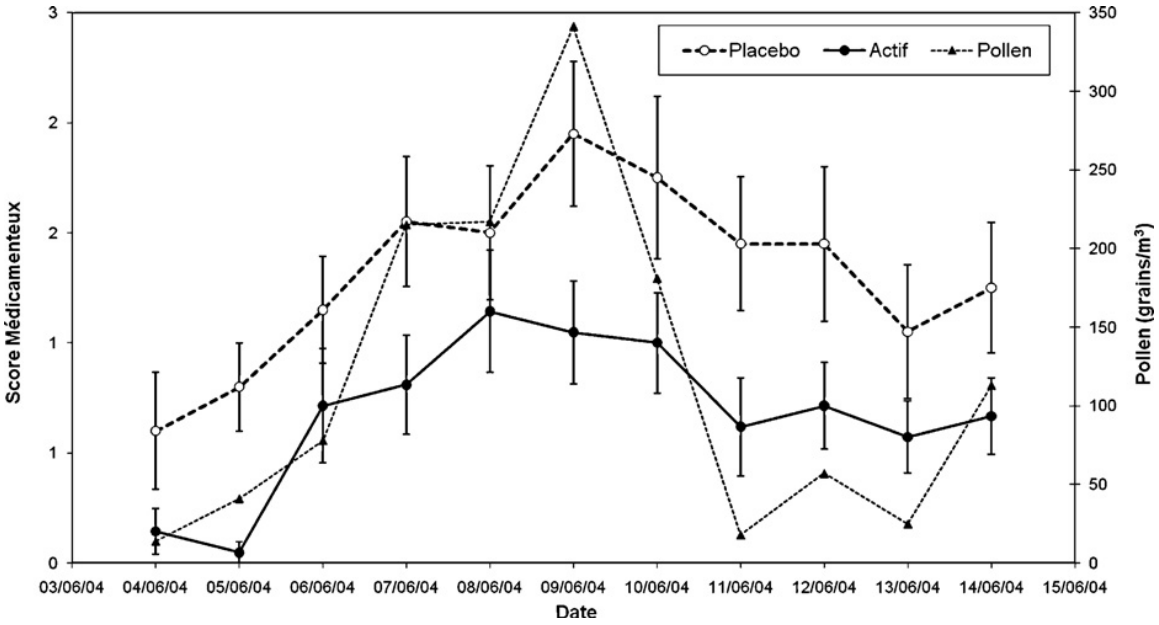


**Figure 4 Over-time modification of grass pollen levels and global efficacy score (T5SS corrected with RM score) (mean ± standard deviation) in the active and placebo groups during the whole study period**

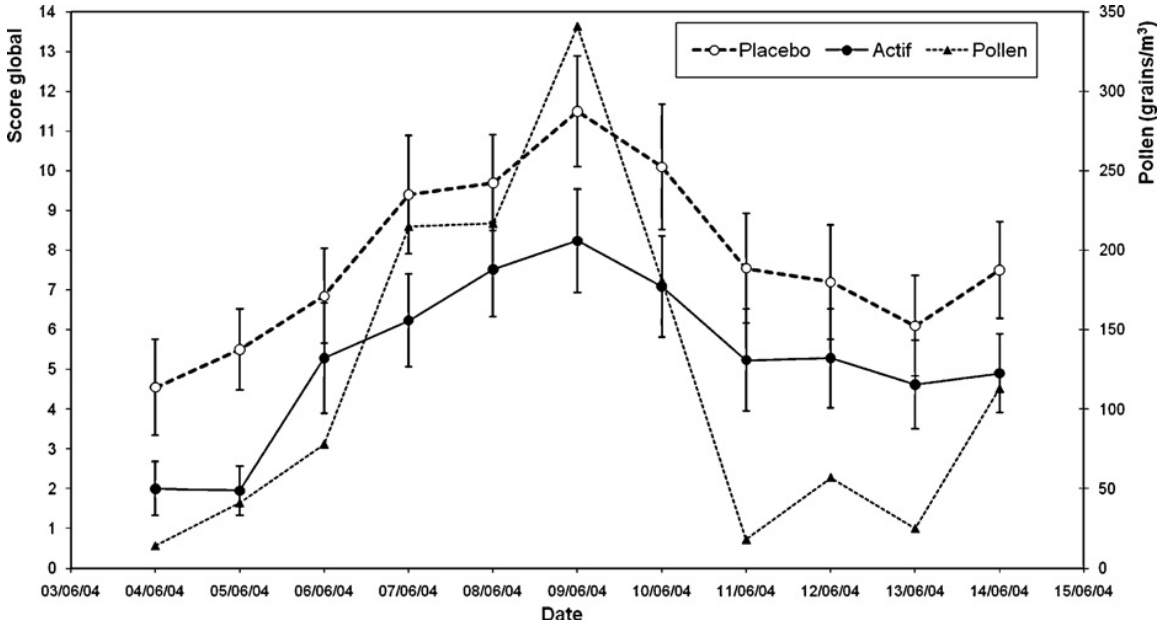



**Figure 5 Over-time modification of grass pollen levels and Quality of Life score (mean ± standard deviation) in the active and placebo groups during the whole study period**

Curve template similar to the previous ones.

## 7.3. Listings

The listings will be generated in accordance with ICH/E3 guidelines.

# 8. REFERENCES

1. X.Van der Brempt et al. Revue française d'allergologie. 51(2011) 430-436
2. Clark J, Schall R. Assessment of combined symptom and medication scores for rhinoconjunctivitis immunotherapy clinical trials. Allergy 2007;62:1023–8.