# 2 SYNOPSIS

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| Name of Sponsor/Company: Anergis S.A.<br>Name of Drug Product: AllerT<br>Name of Drug Substance: Contiguous overlapping peptides (COPs) of synthetic origin derived from Bet v 1 | Individual Trial Table Referring to Clinical Part of the Dossier<br>Volume:<br>Tab Divider | *(For National Authority Use only)* |
| **Title of Trial:** A multicentre, double-blind, placebo-controlled, randomized trial to assess the efficacy and tolerability of two dosing regimens of AllerT, a combination of contiguous overlapping peptides derived from Bet v 1, in adult subjects allergic to birch pollen | | |
| **Indication:** Moderate to severe allergic rhinoconjunctivitis due to birch pollen | | |
| **Coordinating Investigator:** François Spertini, MD, Division of Immunology & Allergy, Centre Hospitalier Universitaire Vaudois (CHUV), 1011 Lausanne, Switzerland | | |
| **Trial Centers:** Conducted at 23 centers in Europe: Denmark (3), France (2), Latvia (2), Lithuania (4), Poland (8), Sweden (3), and Switzerland (1) | | **Publication (reference):** Spertini F et al. Abstract, American Academy of Allergy, Asthma & Immunology, 28 Feb to 4 Mar 2014,San Diego, CA |
| **Trial Period:**<br>First subject randomized: 3 November 2012<br>Last subject completed: 14 June 2013 | | **Phase of Development:**<br>II |

**Objectives:**

***Primary objective:*** To demonstrate the efficacy of 2 months pre-seasonal treatment with AllerT at a maintenance dose of 100 µg in reducing symptoms of allergic rhinoconjunctivitis during the following birch pollen season

***Secondary objectives:***

- To demonstrate the efficacy of 2 months pre-seasonal treatment with AllerT at a maintenance dose of 50 µg in reducing symptoms of allergic rhinoconjunctivitis during the following birch pollen season
- To evaluate the safety and tolerability of 2 months pre-seasonal treatment with AllerT at maintenance doses of 100 µg and 50 µg
- To evaluate the effects of 2 months pre-seasonal treatment with AllerT at maintenance doses of 100 µg and 50 µg during the following birch pollen season on:
  - Subjects' quality of life
  - Other clinical endpoints including night-time symptoms, number of well days, number of days with severe symptoms, and subject's global evaluation of

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| treatment efficacy |
| **Methodology:** Multicenter, international, randomized, double-blind, placebo-controlled, parallel-group trial of 2 maintenance doses (100 and 50 µg/injection) of AllerT.<br><br>The study consisted of a screening visit (V0, 7 to 30 days before randomization), a treatment period (5 injections [at V1, V3, V5, V7, V9] over ≥ 8 weeks with a safety follow-up visit [V11] 28 to 31 days after the last injection), and a clinical assessment period (over the following birch pollen season, with visits V12 scheduled 25 to 35 days prior to the expected peak of the birch pollen season, V13 scheduled 7 to 14 days after the expected peak, and V14 scheduled within 2 weeks after the actual end of the season).<br><br>The actual birch pollen season was determined for each center using regional pollen data, with the start defined as the first of 3 consecutive days with a regional pollen count ≥ 10 grains/$m^3$ and the end defined as earliest between the $42^{nd}$ day after the start of the season and the last day in the last occurrence of 3 consecutive days with a regional pollen count > 10 grains/$m^3$. |
| **Number of Subjects (Planned and Analyzed):** Planned: 306 subjects (102 per treatment group, with 10 to 20 subjects per study center). Enrolled/analyzed: 240 subjects enrolled; 239 received randomized treatment (79 placebo, 78 AllerT 50 µg, 82 AllerT 100 µg; analysis of safety) and 211 (71, 70, and 70, respectively) were included in the Modified intent-to-treat (ITT) set (primary analysis of efficacy). Due to slower than expected recruitment, fewer subjects than planned hd been enrolled when it was necessary to stop recruitment to allow sufficient treatment time before the start of the birch pollen season. |
| **Diagnosis and Main Criteria for Inclusion:** Men and women aged 18 to 55 years with moderate to severe allergic rhinoconjunctivitis to birch pollen during the 2 preceding birch pollen seasons confirmed at screening by a rhinoconjunctivitis symptom score (RSS) ≥ 12 and previous use of anti-allergy medication during the 2 preceding birch pollen seasons and positive tests with birch pollen extract (skin prick test) and Bet v 1 (specific immunoglobulin [Ig] E CAP test) at screening. |
| **Test Product(s) and Batch Number(s):**<br><br>AllerT 2X (100 µg): 250 µg/mL in 0.5-mL aliquots of sterile 0.9% NaCl solution, Batch number M7.12.044<br>AllerT 2X (50 µg): 125 µg/mL in 0.5-mL aliquots of sterile 0.9% NaCl solution, Batch number M7.12.042<br>Adjuvant: 2 mg/mL $Al(OH)_3$ in 0.7-mL aliquots of sterile 0.9% NaCl solution, Batch number M7.12.048<br><br>AllerT 2X was an equimolar mix of 3 COPs (AllerT1, AllerT2, and AllerT3) of synthetic origin derived from the Bet v 1 sequence of birch pollen provided at twice the needed concentration. Before administration, AllerT 2X was mixed with an equal volume of supplied adjuvant to provide 125 and 62.5 µg/mL AllerT in 1 mg/mL $Al(OH)_3$ and 0.9% NaCl. |
| **Test Product(s) Dose, Route, Regimen, and Duration:**<br><br>Group A Starting dose: 50 µg/injection |

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| | Maintenance dose: | 100 µg/injection |
| Group B | Starting dose: | 25 µg/injection |
| | Maintenance dose: | 50 µg/injection |

Randomized treatment was administered by a trained physician at the study center via subcutaneous (SC) injection given in the deltoid area, with each injection in alternating arms. On Study Day 0, subjects received a single 0.4-mL injection of randomized treatment (starting dose). Subsequent 0.8-mL injections of randomized treatment (maintenance dose) were administered on Study Days 7, 14, 28, and 56 (set as Days 1, 8, 15, 19, and 57 for analysis) with at least 7 days between injections. The dose could remain at or be down-titrated to the starting dose in case of systemic allergic reaction or decreased forced expiratory volume during the first second of expiration [FEV1]).

**Reference Therapy and Batch Number(s):**

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| Placebo: | 0.9% NaCl solution in sterile 0.5-mL aliquots, Batch number M7.12.040 |
| Adjuvant: | 2 mg/mL $Al(OH)_3$ in 0.7-mL aliquots of sterile 0.9% NaCl solution, Batch number M7.12.048 |

Before administration, placebo was mixed with an equal volume of supplied adjuvant (final solution 1 mg/mL $Al(OH)_3$ in 0.9% NaCl).

**Reference Therapy Dose, Route, Regimen, and Duration:**

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| Group C | Placebo treatment administered in the same manner as AllerT. |

**Criteria for Evaluation:**

Efficacy:

*Primary variable:* Average of the combined rhinoconjunctivitis symptom and medication score (RSMS) obtained daily during the birch pollen season (from the actual start to the actual end days, inclusive)

*Secondary variables:*

- Average of the quality-of-life total score obtained weekly during the birch pollen season (from the actual start to the actual end days, inclusive)
- Average of the night-time nasal symptom score (NNSS) obtained daily during the birch pollen season (from the actual start to the actual end days, inclusive)
- Average of the combined rhinoconjunctivitis and night-time symptom and medication score (RNSMS) obtained daily during the birch pollen season (from the actual start to the actual end days, inclusive)
- Percent of well days during the birch pollen season when the daily questionnaires were completed (from the actual start to the actual end days, inclusive)
- Percent of days with severe symptoms during the birch pollen season when the daily questionnaires were completed (from the actual start to the actual end days, inclusive)
- Subject's global evaluation of treatment efficacy score recorded at Visit 14 (V14)

*Exploratory variables:*

- Changes from baseline (V1) to post-treatment visits (V11, V13, and V14) in serum

Bet v 1-specific IgG4 and Bet v 1-specific IgE

- Average of the combined asthma symptom and medication score (ASMS) obtained daily during the birch pollen season (from the actual start to the actual end days, inclusive)
- Average of the combined rhinoconjunctivitis and asthma symptom and medication score (RASMS) obtained daily during the birch pollen season (from the actual start to the actual end days, inclusive)

Safety:

- Occurrence of immediate systemic allergic reactions after each SC injection of randomized treatment
- Occurrence of treatment-emergent adverse events (AEs, i.e., occurring after the 1st injection on V1 up to the later of V11 or 28 days after the last injection)
- Occurrence of death during the study (V1 through V14)
- Occurrence of treatment-emergent serious AEs (SAEs, occurring after the 1st injection on V1 up to the later of V11 or 28 days after the last injection)
- Occurrence of AEs that led to premature discontinuation of randomized treatment
- Changes from baseline (V0) to V11 in clinical laboratory safety variables
- Occurrence of clinically relevant treatment-emergent marked abnormalities in laboratory safety variables at V11
- Changes in vital signs between pre- and post-injection measurements for each SC injection of randomized treatment
- Occurrence of a > 30% decrease in FEV1 between pre- and post-injection measurements (at 30 min, 60 min, 6 to 8 h, and 24 h) for each SC injection of randomized treatment
- Changes from baseline (V0) to V11 in electrocardiogram (ECG) variables (central reading)
- Occurrence of clinically relevant treatment-emergent ECG findings at V11 (central reading)

**Statistical Methods:** The planned sample size (86 evaluable subjects per treatment group, 258 evaluable subjects in total) would provide 90% power to detect an effect size of 0.5 (a difference from placebo of 0.25 RSMS units, assuming a standard deviation of 0.50 RSMS units) for AllerT 100 µg and 50% power to detect an effect size of 0.3. For AllerT 50 µg, this sample size would provide 81% power to detect an effect size of 0.5, if the 2 doses were equally efficacious. Assuming that 15% of randomized subjects would be excluded from the Modified ITT set, 306 subjects were to be randomized 1:1:1 to the 3 treatment groups.

The first null hypothesis tested was that there is no difference between AllerT 100 µg and placebo treatment groups in the primary efficacy variable. A further null hypothesis subordinated to the first (strict monotonicity of the dose effect assumed) was that there is no difference between the AllerT 50 µg and placebo treatment groups in the primary

variable. Each test performed at a 0.05 2-sided type-I error level provided an overall trial-wise type-1 error of 0.05 (2 sided).

The main analysis of the primary variable tested AllerT 100 µg vs placebo within an analysis-of-covariance (ANCOVA) model, with treatment and predefined geographical regions as independent factors, using the Modified ITT set (no imputation for missing values was required). If the null hypothesis was rejected, the subordinate null hypothesis concerning AllerT 50 µg would be similarly tested. Data were summarized by treatment group using model-derived least squares (LS) means with 95% confidence limits (CL), observed mean and median with 95% CL, standard deviation, standard error, quartiles, minimum, and maximum. Placebo-corrected treatment effects were summarized using LS mean and Hodges-Lehman median differences from placebo, each with 95% CL. Supportive analyses used different analysis sets (All-randomized, Per-protocol, Per-protocol with full treatment), non-parametric tests (Wilcoxon rank-sum without adjustment, ANCOVA on ranks), and excluding subjects with an overall unblinded mean pollen count during the birch pollen season within the first quartile of all such mean values. The individual components of the combined endpoint (i.e., RSS and rhinoconjunctivitis medication score [RMS]) were summarized for the Modified ITT set, with *post-hoc* analyses using the ANCOVA model.

Secondary and exploratory variables were summarized for the Modified ITT set and exploratorily tested in a manner similar to the main analysis of the primary variable without adjustment for multiple testing and with no confirmatory goal. Exploratory analyses by subgroups were also performed on the primary and secondary variables. Anti-Bet v 1 IgG4 and IgE values and the changes from baseline were summarized descriptively and exploratorily. The placebo-corrected treatment effect was summarized using observed mean, geometric mean, median, and median percentage differences from placebo with corresponding CL and tested using the Wilxocon rank sum test. Immunology data were also graphically presented by individual subject and with fold-increases from baseline summarized in box and whisker plots. The ratio of anti-Bet v 1 IgG4 and IgE was similarly graphed; P-values for comparisons of fold-increases were from the Wilcoxon test (t approximation).

Safety and other variables were summarized and compared descriptively, with no statistical inference performed. Treatment-emergent AEs were summarized overall, by injection, and in subgroups defined by a history of seasonal asthma (yes, no). Systemic allergic reactions were additionally summarized by World Allergy Organization (WAO) grade. Non-treatment-emergent AEs (occurring more than 28 days after the last injection) were also summarized.

**Summary and Conclusions:**

Subject Disposition: Of the 240 subjects randomized (79 placebo, 79 AllerT 50 µg, 82 AllerT 100 µg), 1 in the AllerT 50-µg group did not receive treatment, and 13 (0, 3, 10, respectively) did not complete the treatment period. Of the 239 subjects treated, all but 1 on placebo who was lost to follow-up completed the clinical assessment period.

Demographics and Baseline Characteristics: Randomized study subjects were Caucasians from 18 to 55 years of age, with slightly more women than men (51.7% vs 48.3%) and a

% predicted FEV1 ranging from 77.9% to 124.9%. Overall, 65.8% of subjects had a baseline RSS score above the RSS median, and only 15.4% had a history of seasonal asthma. Baseline data were generally similar among the 3 treatment groups and in all analysis sets.

Efficacy Results: In this trial, AllerT 50 µg was efficacious, with nominally significant improvements in primary and secondary endpoints. AllerT 100 µg indicated efficacy on several endpoints but did not appear more efficacious than the 50-µg dose. Both AllerT 50 and 100 µg induced a strong IgG4 response against Bet v 1 while not associated with major changes in anti-Bet v 1 IgE levels.

The combined RSMS was lower with AllerT 100 µg than with placebo, but the main analysis of the primary variable did not find a statistically significant difference (mean treatment effect −0.13, 95% CL −0.31, 0.06; P = 0.1798; ANCOVA). Thus, the null hypothesis for the 100-µg dose could not be rejected, and that for the 50-µg dose could not be formally tested. However, the lower combined RSMS with AllerT 50 µg versus placebo and the planned analysis indicated a clinically relevant treatment effect on the combined RSMS with this dose (mean treatment effect −0.23, 95% CL −0.42, −0.05; P = 0.0146; ANCOVA). Observed median percentage differences from placebo were −19.1% with the 100-µg dose and −29.9% with the 50-µg dose. Results from planned supportive analyses for each dose were similar to those from the main analysis. *Post-hoc* exploratory analyses on the individual RSS and RMS scores used in the combined RSMS indicated that symptoms were improved with both doses, and medication use possibly reduced with the 50-µg dose only.

Results from secondary and exploratory variables were consistent with results from the primary variable. Average quality-of-life scores during the season were lower with both AllerT 50 and 100 µg compared with placebo indicating improved subjective quality of life, with mean treatment effects −0.51, P = 0.0078 and −0.48, P = 0.0110, respectively (ANCOVA), and median percentage differences from placebo of −29.6% and −26.4%, respectively. Similarly, results of the average NNSS indicated improvement in night-time nasal symptoms, with mean treatment effects −0.24, P = 0.0077 and −0.22, P = 0.0138, respectively, and median percentage differences from placebo of −35.8% and −39.8%, respectively. Differences between AllerT 50 µg and placebo observed in the combined RNSMS (mean effect −0.23, P = 0.0115; median percentage difference from placebo −31.5%) and the combined RASMS (exploratory variable; mean effect −0.15, P = 0.0361; median percentage difference from placebo −27.9%) were not seen with the 100 µg dose. Analyses did not indicate a treatment effect in the combined ASMS (exploratory variable), percentage of well days (trend with the 50-µg dose), percentage of days with severe symptoms, or the subject's global analysis of treatment efficacy at study end with either dose. Subgroup analyses of the primary and secondary variables generally reflected those of the population as a whole.

In subjects treated with AllerT, median anti-Bet v 1 IgG4 concentrations increased approximately 20-fold from baseline to V11 (4 weeks after the last injection) and remained elevated throughout the following birch pollen season with no difference between the 2 doses. No change in anti-Bet v 1 IgG4 was observed with placebo at any time point. Median anti-Bet v 1 IgE concentrations increased about 2-fold from baseline to

V11 in AllerT-treated subjects, with no further increase seen at later time points. In contrast, anti Bet v 1 IgE did not increase with placebo treatment (V11) but did increase during and after the following birch pollen season, also by about 2-fold. Thus, AllerT treatment resulted, although with different kinetics, in an increase in anti-Bet v 1 IgE similar to that resulting from the natural exposure to one season with no futher increase.

Safety Results: Most subjects in the study had a treatment-emergent AE and the overall incidence was higher in subjects on AllerT 50 or 100 µg than placebo (89.7%, 85.4%, and 74.7%, respectively) as were the total numbers of different treatment-emergent AEs (285, 321, and 172, respectively) and of treatment-emergent AE reports (479, 513, and 267, respectively). Treatment-emergent AEs were associated with each of the 5 injections, with higher incidences after the 2nd than the 1st injection and particularly in the AllerT groups lower incidences thereafter. In all 3 treatment groups, most treatment-emergent AEs were mild, occurred more than 1 hour after an injection, and were considered related to randomized treatment. No deaths occurred.

Treatment-emergent AEs associated with AllerT treatment (≥ 5% difference from placebo with either dose) were dyspnea, cough, rhinitis, urticaria, chest discomfort, pruritus, rhinorrhea, conjunctivitis, sneezing, nasal obstruction, and allergic rhinitis. Most of these events were systemic allergic reactions and appeared to be dose related (50 vs 100 µg). Those that were immediate or grade-3 occurred only in AllerT-treated subjects as did all SAEs (3 subjects), but there were no grade-3 (WAO grading) immediate systemic allergic reactions (occurring < 30 minutes after an injection). Discontinuation of treatment due to an AE occurred only in AllerT treatment groups, but in more subjects in 100-µg group than the 50-µg group (8 vs 2). Subgroup analysis found no greater risk of AEs in subjects with a history of seasonal asthma than in those without. The occurrence of non-treatment-emergent AEs (occurring at least 28 days after the last injection) showed no relationship to AllerT treatment.

A > 30% decrease in FEV1 following an injection occurred more frequently on AllerT 50 and 100 µg than placebo (10.3%, 12.2%, and 3.8% of subjects, respectively), with most occurring after the 1st and 2nd injections and no clear relationship to the AllerT dose. Small changes in vital signs, clinical laboratory tests, or EGC variables did not appear to be related to AllerT treatment or dose.

Conclusions: Although a definitive explanation for the lack of significant efficacy with the 100-µg dose remains elusive, results of the study in general indicate that a statistically significant treatment effect with the AllerT 50-µg dose compared with placebo might be achieved in future studies. The 2-month AllerT treatment regimen was generally tolerated, with AllerT-related events often dose related with no unexpected safety finding.

Date of Report: 01 April 2014