2.- SYNOPSIS

<table>
<tr><td>Inmunotek</td><td colspan="2">INDIVIDUAL STUDY TABULAR FORMAT</td></tr>
<tr><td colspan="3">Name of Finished Product: Prick Test Betula verrucosa</td></tr>
<tr><td colspan="3">Name of Investigational product substance(s): Allergen extract of the pollen of Betula verrucosa</td></tr>
<tr><td colspan="3">Title of the study:

Betula verrucosa allergen extract. Sensitivity and Specificity Study of prick-test diagnosis preparation.</td></tr>
<tr><td colspan="3">Investigator(s): Manuel Boquete, MD, PhD</td></tr>
<tr><td colspan="3">Study centre(s): Service of Allergy, Hospital “Lucus Augusti” (Lugo, Spain)</td></tr>
<tr><td colspan="3">Publication (reference): N/A</td></tr>
<tr><td colspan="2">Study period: From September 2015 to April 2016

Date of first enrolment: 03/09/2015

Date of last completed: 30/04/2016</td><td>Phase of development :

II-III(dose-finding/confirming)</td></tr>
<tr><td colspan="3">Objectives:

To assess the Sensitivity and Specificity of 4 different concentrations of the skin prick test preparation of Betula verrucosa.</td></tr>
<tr><td colspan="3">Methodology:

Open, prospective, unblinded and non-randomized biological assay. Each patient was tested with four concentrations of allergen and with a histamine and saline solution as positive and negative controls, respectively.</td></tr>
<tr><td colspan="3">Number of subjects:

Two hundred and one subjects were included in the study. There were no dropouts.</td></tr>
<tr><td colspan="3">Diagnosis:

Screening based on subjects already diagnosed as allergic or not to birch pollen.</td></tr>
<tr><td colspan="3">Criteria for inclusion:</td></tr>
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The study was conducted in allergic patients already diagnosed to be “true allergic” to birch pollen (CH+) and patients already diagnosed to be “true non-allergic” (CH-) to birch pollen.

- True positive subjects (CH+) met the criteria of:
  - Clinical history of symptomatology related to the exposure to the environmental presence of the birch pollen.
  - Previous skin prick test positive reaction with the extract of *Betula verrucosa* used as diagnosis in normal clinical conditions in the hospital.
  - Presence of serum specific IgE (CAP System) to the pollen extract of *Betula verrucosa.*
  - Subjects without immunotherapy treatment with an allergen extract of birch pollen.
- True negative subjects (CH-) meet the criteria of:
  - Clinical history of symptomatology related to the exposure to the environmental presence of the pollen of grasses or other perennial allergens (mites, danders) but not to the pollen of birch.
  - Previous skin prick test negative reaction with the extract of *Betula verrucosa* used in as diagnosis in normal clinical conditions in the hospital.
  - Absence or undetectable serum specific IgE (CAP System) to the pollen extract of *Betula verrucosa.*

Patients of both gender aged from 5 up to 70 years.

A mean wheal diameter $\geq$ 3 mm obtained in a prick test with histamine dihydrochloride 10 mg/ml.

Test product, dose, mode of administration:

The investigational product contained the allergen extract of the pollen of *Betula verrucosa* and was tested by administration onto skin. The trial was carried out on the forearm following prick test technique.

The allergen extract of the pollen of *Betula verrucosa* was tested in four concentrations (100, 50, 25 and 10 HEP/mL).

Reference therapy, dose, mode of administration:

Positive control and negative controls were tested onto skin in the same way as the investigational product. The positive control contains histamine dihydrochloride 10 mg/ml in diluent solution and the negative control contained the diluent: NaCl 0.9%, phenol 0.4% and glycerol 50%.

Criteria for evaluation:

The primary endpoint was the positivity or not of the skin prick test. A test was positive when length of the major diameter of the wheal induced by each allergen concentration was ≥ 3mm (corresponding to a wheal size ≥ 7 mm^2).
Statistical parameters evaluated: Evaluation of the parameters of Sensitivity, Specificity, Efficiency, Predictive Positive Value, Predictive Negative Value.
SUMMARY CONCLUSIONS:
EFFICACY RESULTS: The concentrations (50, 25 and 10 HEP/mL) provided 100% specificity and 100 HEP/mL was 99%. Sensitivity was very good with the highest concentrations (100 and 50 HEP/mL) and decreased in the lowest concentrations. The best efficiency values were for 100 and 50 HEP (99%, for both concentrations).
SAFETY RESULTS: No adverse events occurred.
CONCLUSION: Based on this results, the concentration of 50 HEP/mL was chosen as the preparation for *in vivo* (skin prick tests) diagnosis of allergy to birch pollen.