2. SINOPSIS

Promotor: Inmunotek	**Specific table of the study that refers to a part of the file:** **Volume:** **Page:**	**(National authority use only)**
Name of finished product: Bactek®		
Pharmaceutical form: Glycerinated suspension that contains a mixture of six inactivated non-lysated bacterial concentrates		
Study title: Randomised double-blind placebo-controlled, parallel, multi-centre clinical trial of sublingual bacterial vaccine in children with recurrent bronchospasm (wheezing attacks) for the evaluation of efficacy, security and clinical impact.		
Investigators: Antonio Nieto, MD, PhD. (1) Mª José Palao Ortuño MD (2)		
Study centre(s): Hospital Universitario y Politécnico La Fe (1) C/ Bulevar s/n – 46026 (Valencia, España) Hospital de Manises (2) Av. Generalitat Valenciana, 50 - 46940 (Manises, España)		
Publication (reference): N/A		
Study period (years): **Date of first enrolment:** October 2012 **Date of last completed:** May de 2016	**Phase of development:** III	
Objectives: To evaluate the efficacy of a bacterial vaccine, administered daily onto the sublingual mucosa to prevent bronchospasm (wheezing attacks -WA-) episodes, in patients with bronchospasm episodes due to respiratory tract infections, compared with placebo.		
Methodology: Prospective, randomised, double blind, parallel, multicentre and placebo-controlled clinical trial. The study had 6 visits, a baseline visit and 5 programmed visits. The baseline visits of each patient were made between the months of September and March, at that time, they were randomized. The study lasted 12 months per patient. In the first 6 months each patient received the treatment (active or placebo) through sublingual route, applying two sprays daily. The other 6 months of the trial were follow-up of each patient. All patients received the first dose at the Hospital, in order to teach their parents or legal representatives how to administrate the vaccine. The rest of the doses were administrated at the subject's home. In all the visits, except for visit 5, the patient's diaries were given for the evaluation of symptoms, annotation of concomitant medication and health resources consumed.		

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Number of subjects:
Planned patients: 120
Patients included: 121
Analysed patients: 120

Diagnosis, inclusion and exclusion criteria:
Bronchospasm episodes (wheezing attacks) due to respiratory tract infections

Criteria for inclusion:

1. Subjects whose parents/legal representative have given written informed consent.
2. Both gender
3. Subject up to 36 months of age.
4. Subjects with recurrent bronchospasms (wheezing attacks); 3 or more exacerbations in the last 12 months

Criteria for exclusion:

1. Subjects whose parents/legal representatives had not given written informed consent.
2. Subjects out of aged range
3. Subjects who had malignancies or chemotherapy treatment
4. Subjects who were included in another clinical trial in the last 12 months.
5. Subjects who were in immunosuppressive or immunostimulatory treatment
6. Subjects who had received iv gamma globulin in the past 12 months.
7. Subjects who were diagnosed with candidiasis or fungal recurrent infections.
8. Subjects who were diagnosed with malabsorption syndrome
9. Subjects who had clinical allergy to common aeroallergens in the geographical area.
10. Subjects who had hepatitis virus infections, HIV and tuberculosis

Investigational Medicinal Product: (Bactek®) *Staphylococcus aureus* (15%), *Staphylococcus epidermidis* (15%), *Streptococcus pneumoniae* (60%), *Klebsiella pneumoniae* (4%), *Moraxella catarrhalis* (3%) and *Haemophilus influenzae* (3%).
Dosage: 2 spray puff
Administration route: Sublingual
Batches:
12Y44G (SLG-002-01-01)
14E46G (SLG-002-02-01)

Treatment period: 6 months.

Reference treatment: Placebo (Glycerol 50%, pineapple essence s.q. 1 mL, sodium chloride 9mg/mL and physiologic saline solution s.q. 1 mL).
Dosage: 2 daily spray puff
Administration route: Sublingual
Batches:
12Y68G (SLG-002-01-01)
14E47G (SLG-002-02-01)

Criteria for evaluation:
Efficacy
Primary Outcome Measures:

- Recurrent bronchospasm (wheezing attacks) during a period of 12 months after the initiation of the treatment. The number of bronchospasm (wheezing attacks) episodes between control and placebo groups were compared.

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Secondary Outcome Measures:

- Symptom (SS) and medication (MS) scores and the combination of both (SMS) during the WA
- Symptom (SS) and medication scores (MS) and the combination of both (SMS) during all the study
- Health resources consumption. The unscheduled visits to health centre, emergency service visits, days of hospitalization and cost thereof, complementary tests, phone calls to the doctor or paediatrician were counted per patient.
- Social resources. The absenteeism from nursery, the need of caregivers to the child at home and during hospital admissions were evaluated.
- Evaluation of modified Composite Asthma Severity Index (CASI) score (5 domains) and the Visual Scale.

Safety:

All adverse events were recorded. All were individually evaluated to assess severity and to classify them as probably related or unrelated to the study medication.

Statistical methods:

The Research and Clinical Epidemiology Unit, Department of Preventive Medicine of San Carlos University Hospital (Madrid, Spain) and the Medical Department of INMUNOTEK S.L. carried out the statistical analysis The Excel spreadsheet (Microsoft, Inc. USA) with the XlStat Add-in (Addinsoft, France), SPSS 20 (IBM Corp., USA) and STATAs 12.0 (StataCorp, USA) software were used. All outcomes, except for weight and height, followed a non-normal distribution. Therefore, parametric or non-parametric tests were used for analysis. The Hodges-Lehmann estimator was used to measure the effect size of the differences between the two groups. The Number Needed to Treat (NNT) was calculated based on the number of patients to be treated to prevent
one case of recurrent wheezing (three or more WA) during the study. The Kaplan-Meier estimator was used to compare time until appearance of first WA after initiation of treatment and after discontinuation of treatment 6 months later. Cox model was adjusted to evaluate the real effect expressed as a hazard ratio (HR) and its 95% confidence interval (95% CI). In all contrasts the null hypothesis is rejected with $p<0.05$.

The following statistical test procedures were applied to the results:

- Descriptive statistics: mean, standard deviation, 95% confidence interval of the mean, median (95% CI), first and third interquartile of the median (interquartile range –IQR-) and the ratio of the results at baseline and at the end.

Comparative statistics. Comparison between groups:

- Shapiro-Wilk was conducted to estimate if the distribution of the outcomes followed a normal distribution or not.
- Intergroup comparison: Mann-Whitney's test for the outcomes that followed a non-normal distribution. Student's t -tests (unpaired data) for those outcomes that followed a normal distribution.
- Hodges-Lehman estimator (with the 95% lower and upper confidence limits -CL-) was used to measure the effect size of the differences between the two groups. This test was performed following Helsel and Hirsch; and Kirchner (1, 2).
- Intragroup comparison: Freidman's test (with the Nemeni procedure for pairwise comparisons) were used to compare the results obtained in each group and in each point of evaluation.

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- All the tests were repeated considering the “worst situation”. This was considering that all the patients who withdrew from the study had continued until the end in it and had not had any improvement or worsening with the vaccine, having the same result at baseline and at the end.

Summary conclusions:

EFFICACY RESULTS:

The number of WA was 176 in the active group and 299 in the placebo, with a median of 3 and 5, respectively (p<0.001), 40% improvement of MV130 over the placebo. The days with WA (19 vs. 42) and the median duration of these WA (6.0 vs. 7.7), were significantly lower in the active group as well as the SMS during the WA. Patients free of new WA were 6 in the active and 0 in placebo (p=0.029); children continuing having recurrent wheezing (≥ three WA/year) were 36 (58%) in the active, and 45 (80%) in the placebo group (p=0.009). The NNT to prevent one case of recurrent wheezing was 5 (95% CI: 2.6–16.1).

There were significant differences in the number of days until the appearance of the first WA after initiation of treatment in the active group compared to placebo (41.0 vs. 5.0 days, respectively). Likewise, there were differences in the same outcome (180.0 vs. 44.5 days, respectively) during the observational post-treatment period.

There was a significant reduction of WA in both groups when compared to baseline. The median of monthly WA before the study was 0.67 and 0.75 for the active and placebo groups, respectively (p=0.053). At the end of the study, the Figure were 0.25 and 0.42 (p<0.001), meaning an intragroup improvement of 63% and 44%, respectively.

The SS, MS and their combination (SMS) considered throughout all the study period were also significantly lower in the active group for almost all variables, with differences over 38% when considering global combinations.

In the evaluation of the “worst case scenario”, there was a small reduction in the statistical estimators, in which the active group still showed a highly significant difference in the analysed outcomes.

There was a significant reduction in telephone calls to the paediatrician, in school absenteeism and caregiver-days, but not in the rest of health and social resources.

The evaluation of modified Composite Asthma Severity Index (CASI) score (5 domains) and the Visual Scale demonstrated that at baseline there were no difference between both groups. From visit 2 to the end of the study (the rest of the visits) the differences between both groups were significant. The evaluation of the follow-up of each group showed that the improvement in both groups was significant.

SAFETY RESULTS:

No adverse reactions were recorded. A total of 166 adverse events were registered, none of them related with the Investigational Medicinal Product, 81 in active group and 85 in placebo group. The difference between both groups was not consider statistically significant. These adverse events are common pathologies in infants: 155 were classified as mild, 10 as moderate and 1 as severe (one patient of the placebo group presented seizure crisis and his parents decided to withdraw the study).

CONCLUSION:

Immunotherapy with a sublingual bacterial preparation formulated with a defined composition of heat-inactivated whole-cell bacteria is safe and prevents wheezing episodes in young children.