NAME OF COMPANY: Inmunotek, S.L.	INDIVIDUAL STUDY TABULAR FORMAT
NAME OF FINISHED PRODUCT: Bactek	
NAME OF INVESTIGATIONAL PRODUCT SUBSTANCE(S): MV130	
TITLE OF THE STUDY Randomized double-blind placebo-controlled prospective, parallel, multicenter clinical trial of bacterial polyvalent vaccine (BACTEK®) administered by sublingual mucosa in subjects with chronic obstructive pulmonary disease (COPD) for efficacy evaluation, safety, and immunomodulatory response.	
PRINCIPAL INVESTIGATORS Eduardo Fernández Cruz, MD, PhD; Study Coordinator. Hospital Gregorio Marañón. Javier Miguel Díez, MD; Principal Investigator. Hospital Gregorio Marañón. José Luis Álvarez-Sala, MD, PhD; Principal Investigator. Hospital Clínico San Carlos. María Jesús Buendía, MD; Principal Investigator. Hospital Infanta Leonor. Carlos José Álvarez, MD; Principal Investigator. Hospital 12 de Octubre. Soledad Alonso, MD; Principal Investigator. Hospital Torrejón de Ardoz. Francisco García, MD; Principal Investigator. Hospital La Paz. Joan Serra, MD; Principal Investigator. Hospital de Vic.	
STUDY CENTER(S) 1. Hospital General Universitario Gregorio Marañón (HGUGM), Madrid, Spain, 28007. 2. Hospital Clínico San Carlos (HCSC), Madrid, Spain, 28040. 3. Hospital Universitario Infanta Leonor, Madrid, Spain, 28031. 4. Hospital Universitario 12 de Octubre, Madrid, Spain, 28041. 5. Hospital Universitario de Torrejón de Ardoz, Madrid, Spain, 28850. 6. Hospital Universitario La Paz, Madrid, Spain, 28046. 7. Hospital Universitario de Vic, Barcelona, Spain, 08500.	
PUBLICATION (reference): NA.	
STUDY PERIOD: 18 months per subject. **DATE OF FIRST ENROLMENT:** 6th May 2013. **DATE OF LAST COMPLETED:** 29th July 2019.	**PHASE OF DEVELOPMENT:** II/III
OBJECTIVES The main objective of this trial is to evaluate the efficacy and safety of a bacterial vaccine administered sublingually in comparison with placebo in subjects with moderate and severe COPD based on the number of COPD exacerbations.	
METHODOLOGY A multicenter, prospective, randomized, double-blind, parallel-group, placebo-controlled phase II/III clinical study. The study included 7 visits: a baseline visit (BV) and 6 programmed visits. In some cases, BV and V1 were done at the same time. The baseline visits took place between May 2013 and January 2018.	

The study lasted 18 months per subject. In the first 12 months, each subject received the blind treatment (active or placebo) through the sublingual route applying two sprays daily. The last 6 months corresponded to the follow-up period.

- Subjects in Group I received active treatment consisting of a bacterial vaccine administered sublingually for 12 months (i.e., MV130 12M).
- Subjects in Group II received placebo sublingually for 12 months. The composition of this placebo was identical to the bacterial vaccine, but it did not contain the drug substance.

Ratio between groups was 1:1.

All subjects received the first dose at the hospital and were trained in the proper administration of the drug. The subsequent doses were administered at the subjects' home.

In all the visits, except for BV and visit 5 and 6, subjects received diaries for the evaluation of symptoms, annotation of concomitant medications and consumption of healthcare resources. In visits 2 to 6 subject's diaries were collected.

NUMBER OF SUBJECTS

The planned number of subjects to be included in the trial was 180.

The number of subjects that were included in the study was 198.

The number of subjects who were randomized (excluded screening failures) were 198 and those who completed treatment and follow-up were 142.

Analyzed sets:

- Efficacy evaluable population (Intention-to-treat): 198.
- Efficacy evaluable population (per-protocol): 142.
- Safety evaluable population: 198.
- Immunological sub-study: 60.

DIAGNOSIS

Subjects with a diagnosis of moderate or severe COPD according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guideline classification.

CRITERIA FOR INCLUSION

- Subjects who had provided their written informed consent.
- Subjects of both sexes.
- Subjects aged between 35 and 85 years.
- Subjects who were capable of complying with the dosing regimen.
- Subjects with a diagnosis of moderate or severe COPD according to the GOLD criteria.
    - Subjects with a predicted post-bronchodilator force expiratory volume in the first second (FEV1) <50% (50% -30%), with or without chronic symptoms (e.g., coughing or sputum production).
- Subjects who had experienced at least three moderate exacerbations (i.e., those requiring treatment with antibiotics, systemic corticosteroids, or both, as prescribed by their general practitioner or pulmonologist in the standard consultation and/or the Emergency Department of their Clinic) or two exacerbations with at least one requiring hospitalization due to a COPD exacerbation and the other one a moderate exacerbation occurred within the last year.

- Subjects who had not changed their medication for the maintenance treatment of COPD within the past 6 months.
- Subjects with an accumulated consumption of ten or more pack-years. The subjects may or may not be active smokers.
- The subjects included in the trial must live in the Autonomous Community of Madrid throughout the study period.
- Subjects included in the trial may had been vaccinated with pneumococcal polysaccharide vaccine at least 4 weeks before starting the administration of the study medication.
- Women of childbearing age had to use an approved method of contraception (oral, vaginal, transdermal, intrauterine device [IUD], etc. or barrier methods) and obtain a negative result in the urine pregnancy test performed during the screening visit.

CRITERIA FOR EXCLUSION

- Subjects outside the allowed age range.
- Subjects who were unable to cooperate and/or had a severe psychiatric disorder.
- Women who were pregnant, breastfeeding, expected to become pregnant during the study (including assisted reproduction), or who refused to use contraceptives during the study (including barrier methods). Women who became pregnant during the clinical trial had to discontinue their participation in it.
- Subjects who had participated in a study or clinical trial with an investigational product within the 3 months preceding their inclusion in this study.
- Subjects diagnosed with asthma based on the guidelines of the American Thoracic Society and the European Respiratory Society. If the investigators were unable to differentiate between COPD and asthma, a bronchodilator test with inhaled salbutamol must be performed, excluding those subjects with FEV1 changes >400 mL.
- Subjects with a diagnosis other than COPD that causes them to have an unstable condition or a life expectancy <3 years.
- Subjects who experienced a COPD exacerbation within 4 weeks prior to the start of the trial.
- Subjects with moderate COPD who required treatment with inhaled corticosteroids in the last 4 weeks.
- Subjects with moderate COPD who received systemic corticosteroids (orally, intramuscularly, or intravenously) in the last 4 weeks.
- Subjects diagnosed with a Primary (European Society for Immunodeficiencies [ESID] guidelines) or Secondary Immunodeficiency within the 12 months preceding their inclusion in the clinical trial or the trial's baseline visit.
- Subjects diagnosed with a chronic lymphoproliferative disease.
- Subjects diagnosed with a chronic infectious disease (tuberculosis [TB], HCV, HIV, or HBV).
- Subjects with chronic heart disease, arrhythmias, or episodes of arrhythmia secondary to the use of bronchodilators.
- Subjects diagnosed with COPD and chronic colonization by *Pseudomonas aeruginosa.*
- Subjects with COPD and bronchiectasis diagnosed by CT imaging before the age of 40.
- Subjects diagnosed with very severe COPD according to the GOLD classification.
- Subjects requiring home oxygen therapy or non-invasive mechanical ventilation.
- Subjects with a history of hypersensitivity to any of the vaccine's components.

- Subjects receiving immunosuppressive treatment with azathioprine, methotrexate, ciclosporin, cyclophosphamide, tacrolimus, antimalarial drugs, or gold salts.
- Subjects who have been treated with monoclonal antibodies such as rituximab or TNF-alpha inhibitors in the last 6 months.
- Subjects receiving chronic treatment with azithromycin or inhaled antibiotics (tobramycin or colistin).

TEST PRODUCT, DOSE, MODE OF ADMINISTRATION, BATCH NO.

The trial medication was a polyvalent bacterial vaccine; the pharmaceutical form was a glycerinated suspension containing a mixture of six inactivated non-lysate bacterial concentrates (V104 *Streptococcus pneumoniae* 60%, V101 *Staphylococcus epidermidis* 15%, V102 *Staphylococcus aureus* 15%, V113 *Klebsiella pneumoniae* 4%, V105 *Moraxella catarrhalis* 3%, V103 *Haemophilus influenzae* 3%) as active substances. As excipients, it contained for 1 ml: 0.63 g of glycerol, artificial pineapple flavoring (0.01 mL), sodium chloride (9 mg) and water (q.s. for 1 mL).

The sublingual administration consisted of a daily, pump-metered dose of 0.1 mL per puff, sprayed twice under the tongue.

To complete the treatment, 13 bottles of 9 mL each were given to each patient, packed in boxes.

The strength and batches tested were as follows:

- 13E01G (SLG-001-01-01; SLG-001-01-02; SLG-001-01-03; SLG-001-01-04). 300 FTU (Formazin Turbidity Units).
- 13S35G (SLG-001-02-01; SLG-001-02-02). 300 FTU (Formazin Turbidity Units).
- 13N45G (SLG-001-03-01). 300 FTU (Formazin Turbidity Units).
- 13D86G (SLG-001-04-01). 300 FTU (Formazin Turbidity Units).
- EC0301G15Y (SLG-001-05-01). 300 FTU (Formazin Turbidity Units).
- A17L70G (SLG-001-06-01). 300 FTU (Formazin Turbidity Units).
- A17D73G (SLG-001-06-01). 300 FTU (Formazin Turbidity Units).
- A17S108G (SLG-001-07-01). 300 FTU (Formazin Turbidity Units).

TREATMENT DURATION

Subjects received daily sublingual treatment for 12 months, either active or placebo as stated above (*See Methodology section*).

REFERENCE THERAPY, DOSE, MODE OF ADMINISTRATION, BATCH NO.

The control product was placebo.

It contained an identical solution to the test product with no active substances (without the inactivated non-lysate bacterial concentrates), and was administrated through the sublingual route, applying two sprays daily.

The composition contained for 1 ml: 0.63 g of glycerol, artificial pineapple flavoring (0.01 mL), sodium chloride (9 mg) and water (q.s. for 1 mL).

The batches tested were as follows:

- 13E02G (SLG-001-01-01; SLG-001-01-02; SLG-001-01-03; SLG-001-01-04).
- 13S36G (SLG-001-02-01; SLG-001-02-02).
- 13N46G (SLG-001-03-01).
- 13D87G (SLG-001-04-01).
- EC0302G15Y (SLG-001-05-01).
- EC0101G17L (SLG-001-06-01; SLG-001-07-01).

CRITERIA FOR EVALUATION

EFFICACY

Primary outcome variable: number of COPD exacerbations

- Primary efficacy analysis was based on the comparison of the number of COPD exacerbations during the 18 months of the study (12 of treatment + 6 of follow up) in the MV130 group vs placebo.

Secondary efficacy endpoints/analyses:

- Decrease in the rate of COPD exacerbations per study group at 12 months (end of the trial treatment) and 6 months after treatment termination (follow-up).
- Decrease in the severity of the COPD exacerbations. The severity of the exacerbations was measured based on the consumption of healthcare resources (i.e., visits to the Emergency Department, hospitalizations, or consultations).
- Time elapsed between the start of the treatment and the first COPD exacerbation.
- Use of drugs (antibiotics, corticosteroids, etc.).
- Number of hospitalizations due to COPD exacerbations.
- Days of hospitalization due to COPD exacerbations.
- Number of visits to the Emergency Room.
- Number of unscheduled medical consultations due to COPD exacerbations.
- Health-related quality of life, as determined by an adapted version of the specific CAT test.
- Healthcare expenditure resulting from resource consumption during episodes of COPD exacerbations occurring during the trial period.
- Variations (change between the baseline level and months 3, 6, and 12, as well as in comparison with the placebo) in the following immunological parameters in the patients participating in the immunological sub study (N = 60) and/or those of the subgroup of the induced sputum study (N = 20) (between month 0 prior to the administration of the vaccine and month 12).
- In a subgroup of patients (n = 20) selected from the group of patients participating in the immunological sub study (n = 60), immunological parameters were evaluated in samples of induced sputum at month 0 (visit 1) and month 12.

SAFETY

- Overall rate, severity, and relationship of any adverse event per administration and patient.
- Assessment of local tolerability (tissular reactions in the administration site).

STATISTICAL METHODS

The statistical analysis was carried out by Cristina Fernández Pérez and Paco López as consultants.

Efficacy analyses were carried out by intention-to-treat (ITT). The primary efficacy variable was assessed in the ITT and per protocol (PP) population. Safety analysis was performed on all randomized subjects (evaluable safety population).

Descriptive analysis of the collected variables was carried out. Depending on the variable nature, the following results were presented:

- Categorical variables were summarized by frequencies and percentages.
- Continuous variables were summarized by means of central tendency and dispersion measures: median, 25% and 75% (Q1 and Q3) percentiles, mean, standard deviation and extreme values (minimum and maximum).

Comparative statistics were performed as follows:

- For two categorical variables, contingency tables with the frequency in each category and the percentage by columns were presented. To evaluate the possible association Fisher's exact test were performed.
- For a numerical variable with a categorical, descriptive statistics were presented by groups. To evaluate the possible association, ANOVA, Mann-Whitney, Wilcoxon, and Kruskal-Wallis nonparametric tests were performed, in accordance with the variable probability distribution.
- Post hoc analyses were also conducted to evaluate pairwise differences once the null hypothesis was rejected.
- Time-to-event data was analyzed by the Kaplan-Meier estimator, and the median and the 25th and 75th percentiles were presented along with their 95% CI, comparing the three curves using the Log Rank test.
- Repeated measures over time including previous and post data were analyzed by Wilcoxon-signed ranked test and Mixed-effects models.

SUMMARY CONCLUSIONS

EFFICACY RESULTS

As primary outcome of the study, the number of COPD exacerbations were significantly reduced in the 18-month efficacy period (12 months treatment + 6 months follow-up period) in subjects receiving MV130 compared to placebo. The median number of COPD exacerbations was 3.0 in the placebo group [IQR, 1.0-5.0] compared to 2.0 [IQR, 1.0-3.0] in the MV130 group ($P<0.01$). The yearly incidence ratio was of 1.82 (95% CI 1.58-2.07) in the MV130 group and 2.61 (95% CI 2.35-3.85) in the placebo group. In addition, MV130 significantly reduced all exacerbations by 30% and decreased severe exacerbations by 49%.

A significant decrease in the rate of COPD exacerbations was also observed at 18 months in the MV130 group compared to placebo. Incidence frequency is described as the number of events in a period of time. The incidence rate for the placebo group was 2.67 compared to 1.86 in the MV130 group ($P<0.001$).

COPD exacerbation severity was assessed by the consumption of healthcare resources including consultation visits, emergency department visits, hospitalization, and ICU hospitalization. Taking this into account, COPD exacerbation severity was found to be significantly reduced in MV130 treated subjects compared to placebo ($P=0.0094$). The median exacerbation severity was 3.0 in the placebo group [IQR, 1.0-23.0] and 1.0 in the MV130 group [IQR, 0.0-5.0].

The time elapsed between the start of treatment and first COPD exacerbation was also assessed. Herein, we can observe the median time to first event in the placebo group is 4.4 months compared to 6.4 months in the MV130 treatment group. These results show how patients undergoing treatment with MV130 have a greater COPD exacerbation-free time.

Use of drugs was another secondary endpoint assessed and was calculated using an index of 1-3 points which included use of antibiotics, inhaled corticosteroids, and systemic corticosteroids, respectively. The median drug use was significantly lower in the MV130 group 24.0 [IQR, 0.0-71.0] compared to the placebo group 40.0 [IQR, 9.0-112.0] (*P*=0.0232). The number and days of hospitalizations due to COPD exacerbations were both found to be significantly reduced in the MV130 treatment group compared to placebo (*P*=0.0319 and *P*=0.0264, respectively). Moreover, in relation to medical assistance, the number of visits to the emergency room were also found to be significantly reduced in the MV130 treatment group (*P*=0.0037). However, no significant differences were found in the number of unscheduled medical consultations due to COPD exacerbations (*P*=0.1008).

Healthcare expenditure resulting from resource consumption during episodes of COPD exacerbations occurring during the trial period was also assessed. Considering the study was not designed to evaluate a pharmacoeconomic impact, a grading system was implemented to evaluate the savings from the use of MV130. This system included: days with medication, visits to healthcare centres and days of hospitalization. A sum of the total resource consumption showed a total score of 8231 in the placebo group compared with 5202 in the MV130 group, showing a 36.8% resource consumption reduction and thus a direct association with a reduction in healthcare expenditure.

Health-related quality of life was assessed by an adapted version of the specific CAT test, which allows an evaluation of the level of impact the disease has on the quality of life of the patient. This was measured in every patient visit, including baseline. The CAT presents a difference of 2.2 points between MV130 and placebo [CI 95%, -4.3, -0.14] at 12 months (*P*=0.037) (treatment period) and of 1.5 points [CI 95%, -3.8, 0.7] at 18 months (full study period). MV130 this way has a positive impact on patients QoL.

Regarding the variations in immunological parameters in a small subset of subjects (immunological sub-study group; n=60), results are currently under evaluation due to their complexity and will be presented in a future report.

SAFETY RESULTS

All safety study analyses were performed on the evaluable safety population, which included all individuals who were randomized (n=198), from those 97 subjects were treated with MV130 and 101 were treated with placebo.

Most of the subjects completed the treatment phase, without experiencing dose reduction, variations in the treatment schedule, or temporary discontinuations of the IMP (referred to as dose reduction, ≤14 days). Other participants did not complete the study because of the following reasons: consent withdrawal (16.6%), lost to follow-up (4.5%), investigator's terminated subjects' participation (3.0%) due to clinical judgement or lack of patient's protocol compliance, and finally, 4.0% were due to adverse events (AEs) that were not related to the IMP.

In the study, 229 AEs were observed in 103 participants (52%), compared to 95 patients who did not experience any AEs (48%). Referring to the number of subjects who had experienced AEs in the study, 113 (48.5%) were from the placebo group and 116 (55.7%) from the MV130 group. Therefore, there were no significant differences between treatment groups (*P*= 0.3234).

From all these AEs, 155 (67.7%) were classified as mild (placebo: 74 [65.5%]; MV130: 81 [69.8%]), 56 (24.5%) as moderate (placebo: 29 [25.7%]; MV130: 27 [23.3%]), and 18 (7.9%) as severe (placebo: 10 [8.8%]; MV130: 8 [6.9%]).

According to the investigators, 216 (94.3%) of the AEs (placebo: 105 [92.9%]; MV130: 111 [95.7%]) were assessed as 'unrelated' and 11 (4.8%) (placebo: 7 [6.2%]; MV130: 4 [3.4%]) as possibly related to COPD. Two (0.9%) of these adverse events (placebo: 1 [0.9%]; MV130: 1 [0.9%]) were assessed as possibly related to the study medication. The two adverse reactions reported were urticaria and pruritus, related to placebo and MV130 respectively. These reactions were already described in the Investigator's Brochure.

Twenty-two AEs (9.6%) were classified as Serious Adverse Events (SAEs), 13 (11.5%) in the placebo group and 9 (0.5%) in the MV130. These SAEs were either unrelated to IMP or related to the baseline disease. No SUSARs were reported during the trial. Three deaths were reported during the study period, 2 in the placebo group (1.8%) and 1 in the MV130 group (0.9%). None were related to the medication.

The most frequently observed AEs were urinary tract infections, upper respiratory tract infections, back pain, and arthralgia. These may be correlated with the demographic characteristics of the population recruited with a median age above 65.0 years for both treatment groups, ranging between 44–84 years.

The safety data obtained in this study for 97 patients with moderate to severe respiratory failure treated with MV130 at a dose of 300 FTU for 12 months showed that the investigational product was safe and had excellent tolerability.

CONCLUSION

In this study, MV130 demonstrated clinical efficacy by reducing the frequency and severity of COPD exacerbations in adult subjects with moderate to severe COPD. MV130 also showed a decrease in healthcare expenditure resulting from a cut off in resource consumption during episodes of COPD exacerbations occurring during the trial period. The study also confirmed no safety concerns for daily sublingual MV130 administration over a period of 12 months in subjects suffering from recurrent COPD exacerbations. This study predicts that the availability of this prophylactic tool could serve as an additional strategy for patients with recurrent COPD exacerbations, minimizing morbidity of these exacerbations, reducing healthcare burden and expenditure, and improving patients' quality of life.